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6 α -METHYLPREDNISOLONE DERIVATIVES

5 The present invention relates to a new class of
6 α -methylprednisolone derivatives, and more particularly
to new 17 α -acyloxy 21-hydroxy- or -acyloxy- 11 β -hydroxy-
6 α -methyl-1,4-pregnadiene-3,20-dione derivatives possess-
ing useful pharmacological activities.

10 In recent years, a number of corticosteroid compounds
have been clinically employed for the purpose of exhibiting
an antirheumatic effect, antiinflammatory effect, anti-
allergic effect and/or antianaphylactic shock effect. Very
recently, the application of corticosteroid compounds has
15 been most widespread as locally effect external drugs
rather than internal drugs in conjunction with their utility
for their antiinflammatory effect, so that various types
of externally applicable corticosteroid drugs are now
commercially available, not only for clinical purposes, but
20 also for general use. A wide variety of corticosteroid
compounds are already known which are derived from hydro-
cortisone, which is regarded as the fundamental compound
of these corticosteroid compounds, by significantly modify-
ing or designing it in such manner that one or more hydroxy
25 groups, methyl groups, halogen (bromine, chlorine or fluorine)

- 2 -

atoms and/or double bonds are introduced into the skeleton structure of the fundamental compound, or the originally existing hydroxy groups are esterified or acetonized.

At the present time, the majority of these steroid compounds are those bearing a fluorine atom at the 9- of 6-position of the fundamental steroid structure. These corticosteroid compounds are certainly excellent corticoid drugs possessing strong pharmacological effects, but on the other hand, involve a problem of safety in connection with the compounds to which the fluorine radical has been introduced, thus necessitating the physicians' particular attention to the clinical use of these compounds. When the metabolism and excretion of these compounds in vivo are taken into consideration, it can hardly be said, depending on the administration term or dose, that no problems arise in respect of safety, even if such compounds are used as externally applied drugs. Although fluorine-containing corticosteroid compounds are still commerciall available as potent antiinflammatory drugs, the use of the compounds themselves for clinical treatment is limited because of their harmful fluorine substituent. Accordingly, an attempt has also been made to develop a new class of corticosteroid compounds free of the harmful fluorine substituent, whilst maintaining their useful pharmacological activities. Such attempts include the chemical modification of the fundamental compound, which, so far reported, is the acylation

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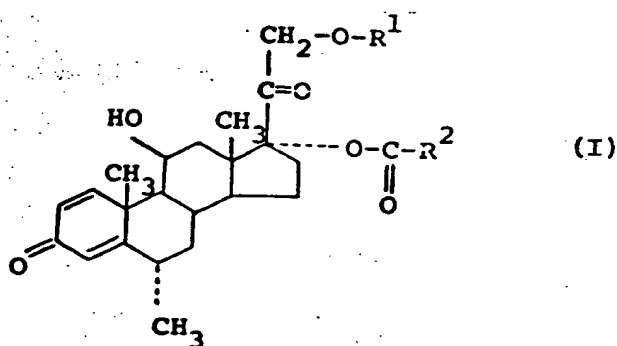
of the hydroxy group originally existing in the basic compounds. For Example, Japanese Laid-open Patent Application Sho.56-86119 discloses 17 α -propionyl-6 α -methylprednisolone and 17 α ,21-dipropionyl-6 α -methylprednisolone obtained by such a modification. This prior art succeeded in the elimination of the harmful fluorine substituent from the steroid molecule, but the result of such a modification revealed only a failure in maintaining the expected pharmacological effects and a very poor improvement in antiinflammatory effect. At the present time, therefore, no steroid compound has been reported or put into practical use as an externally applied strong antiinflammatory drug. Thus, there is still a great demand in this art for further developing a new class of steroid compounds free from any harmful substituents but enhanced in their expected pharmacological activities to a practically acceptable level.

We have now developed a new class of 6 α -methylprednisolone derivatives possessing a strong local anti-inflammatory effect.

As a result of extensive research to develop a new class of corticosteroid compounds free of any harmful fluorine substituent which have a structure similar to the naturally occurring corticosteroid compounds and which exhibit a strong antiinflammatory activity, it has now

been found that new corticosteroid compounds derived from 6 α -methylprednisolone by acylation of its 17 α -hydroxy group with specific acyl reactants are devoid of a harmful fluorine substituent and exhibit a strong local antiinflammatory activity so that these compounds may be used as external antiinflammatory drugs.

Accordingly, the present invention provides a new 6 α -methylprednisolone derivative of the general formula:



wherein R^1 is a hydrogen atom or the group -C-R^3 where R^3

is a straight or once-branched chain C_{1-4} alkyl group, a phenyl group or a lower alkoxy- or alkylthio-methyl group, and R^2 is a straight or once-branched chain C_{1-4} alkyl group, a phenyl group or a lower alkoxy- or alkylthio-methyl group, with the proviso that when R^2 is an ethyl group, R^1 is not a hydrogen atom or R^3 is not an ethyl group.

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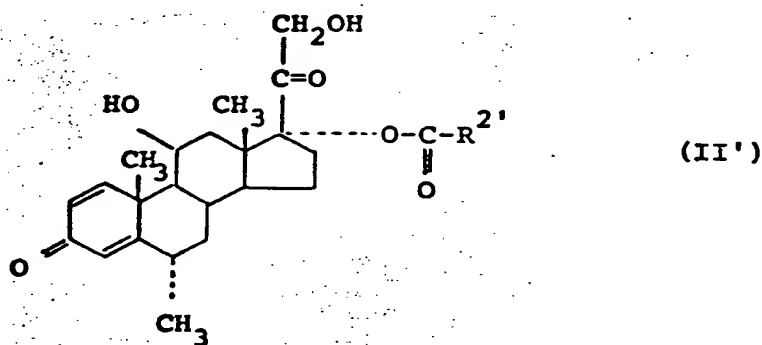
The 6 α -methylprednisolone derivatives of the general formula (I) are 17 α -acyl compounds or 17 α ,21-diacyl compounds depending on the definition of R¹. In the general formula (I), R² and R³ may be the same or different.

Illustrative of the straight or once-branched chain C₁₋₄ alkyl groups are, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl and isobutyl groups. The phenyl group is preferably an unsubstituted phenyl group, but may be a phenyl group substituted on the benzene ring with one or two lower alkyl groups. Examples of the lower alkoxy-methyl group include methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl and n-butoxymethyl group, with methoxymethyl being the most preferred. Examples of the lower alkylthio-methyl group include those corresponding to the above-mentioned alkoxy-methyl groups, in which a sulfur atom is substituted for the oxygen atom. A preferred example of the alkylthiomethyl group is the methylthio-methyl group. By the term "lower alkyl or lower alkoxy group" as used herein, is meant an alkyl or alkoxy group containing from 1 to 4 carbon atoms.

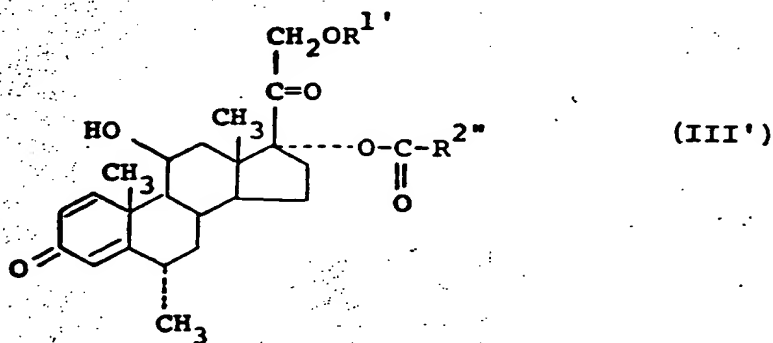
Accordingly, typical examples of the acyl group represented by the groupings $\begin{array}{c} \text{--C--R}^2 \\ \parallel \\ \text{O} \end{array}$ of $\begin{array}{c} \text{--C--R}^3 \\ \parallel \\ \text{O} \end{array}$ include acetyl,

propionyl, n-butyryl, isobutyryl, n-valeryl, isovaleryl, benzoyl, p-methylbenzoyl, methoxyacetyl, ethoxyacetyl, methioacetyl and ethylthioacetyl groups. When R^2 is the same as R^3 , the two groupings -C-R^2 and -C-R^3 represent the same acyl group.

The 6 α -methylprednisolone derivatives of the present invention represented by the general formula (I) are new compounds. Particularly preferred in the present invention are the compounds represented by the general formulae:



and



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In these formulae, $R^{2'}$ is a straight or once-branched C_{3-4} alkyl group, a phenyl group or a lower alkoxy- or alkylthiomethyl group, $R^{1'}$ is the group $\text{-}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{-R}^3$ where R^3

5 has the same meaning as given above, and $R^{2''}$ is a straight or once-branched chain C_{1-4} alkyl group or a lower alkoxy- or alkylthio-methyl group. The present invention particularly relates to those 6α -methylprednisolone compounds of the general formula (I) wherein at least one of the
10 substituents R^1 and R^2 has one of the above mentioned preferred meanings.

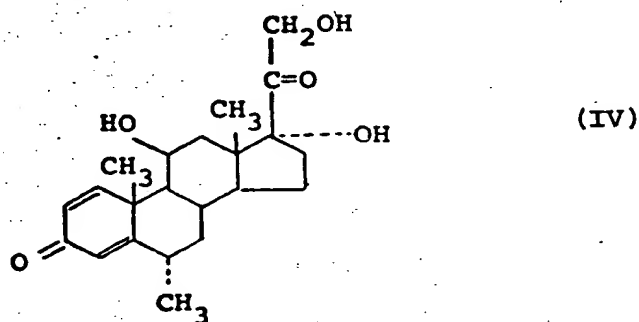
Prednisolone itself is a Δ^1 -derivative of hydrocortisone and has a reduced mineral corticoid activity,
15 which is a side effect of hydrocortisone. A prednisolone derivative obtained by introducing a methyl group into the 6α -position of prednisolone is 6α -methylprednisolone which is 15 to 20% higher in expected activity than the prednisolone itself and is an efficient drug exhibiting
20 outstanding activity against acute and chronic lymphoid leukemia. The compounds of the present invention are 6α -methylprednisolone derivatives carrying a specific acyl group or groups in their 17α -position or $17\alpha,21$ -positions.

25 The new 6α -methylprednisolone derivatives of the present invention can be prepared according to various

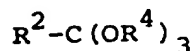
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processes known per se. One of the preferred processes comprises, for example, the following steps:

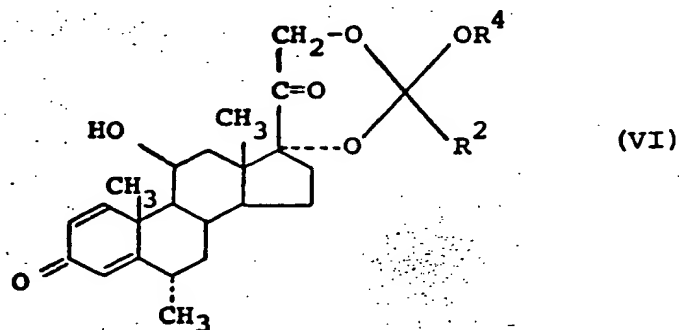
6 α -Methylprednisolone of the formula (IV):



is first reacted with an ortho ester of the general formula:

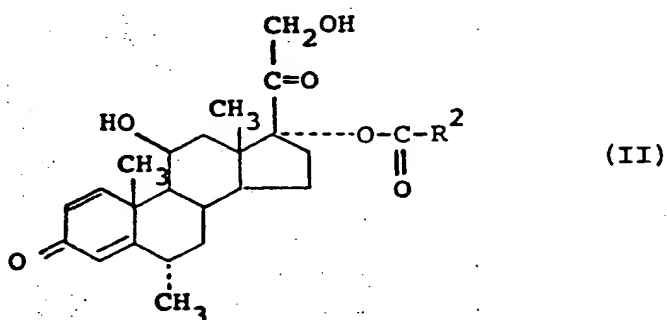


wherein R^2 has the same meaning as given above R^4 is a lower alkyl group, to form a cyclic 17 α ,21-ortho ester of 6 α -methylprednisolone of the general formula:



- 9 -

wherein R^2 and R^4 have the same meaning as given above,
 and then this 17 α ,21-orthoester is subjected to a ring-
 opening reaction to form a 17 α -acyloxy-11 β ,21-dihydroxy-
 6 α -methyl-1,4-pregnadiene-3,20-dione compound of the
 5 general formula:



wherein R^2 has the same meaning as given above.

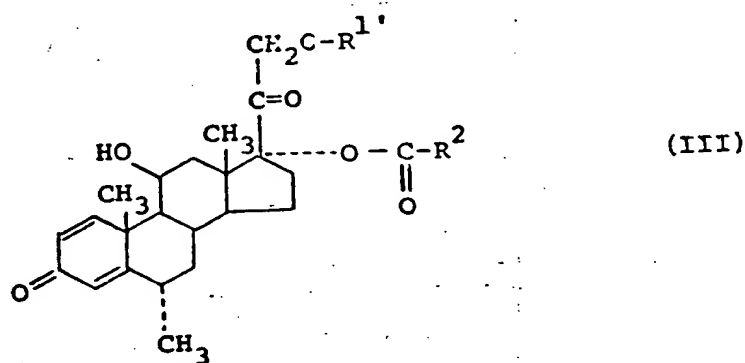
15 If a 17 α ,21-diacyloxy derivative is aimed at as
 the end product, the 17 α -acyloxy-11 β ,21-dihydroxy compound
 of the general formula (II) obtained above is reacted with
 a compound of the general formula



wherein R^3 has the same meaning as given above and X is a
 hydroxyl group, a halogen atom or the group $R^3 - CO - O -$
 where R^3 has the same meaning as given above, to form a
 compound of the general formula:

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- 10 -



wherein $R^{1'}$ and R^2 have the same meaning as given above.

The ortho ester of the formula (V) is suitably selected according to the acyl substituent R^2 to be introduced into the 17 α -hydroxy group of the starting 6 α -methylprednisolone of the general formula (IV). Usually, a methyl or ethyl group is selected as the lower alkyl group R^4 in view of the ease of preparation and availability of the ortho ester. In particular, ethyl or methyl orthoacetate, orthopropionate, orthobutyrate, orthoisobutyrate, orthovalerate, orthoisovalerate, orthobenzoate, orthomethoxyacetate and orthomethylthioacetate may be used.

The compound of general formula (VII) is also suitably selected according to the acyl substituent R^3 -C- to be introduced into the 21-hydroxy group of the 17 α -acyl-6 α -methylprednisolone of the general formula (II) intermediately formed.

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This acylating compound is preferably used in the form of a functionally reactive derivative thereof, such as an acid halide or an acid anhydride in the presence of a base usually selected from a tertiary organic amine, e.g.

5 triethylamine, a pyridine. When the acylating compound of formula (VII) is used as the free acid (i.e. $X=OH$), the acylation is advantageously promoted by adding a dehydrating agent such as a carbodiimide, e.g. *N,N'*-dichlohexylcarbodiimide to the reaction system.

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In detail, the cyclic $17\alpha,21$ -ortho ester of 6α -methylprednisolone of the general formula (VI) is generally prepared by adding an ortho ester of the general formula (V) and a small amount of *p*-toluenesulfonic acid to a
15 solution of 6α -methylprednisolone of the formula (IV) in a solvent and heating the mixture with stirring in an atmosphere of an inert gas or under a current of an inert gas. Illustrative of the solvent for dissolving 6α -methylprednisolone are, for example, inert polar solvents such as dimethylformamide,
20 diethylformamide, dimethylsulfoxide or dioxane. Nitrogen or argon is usually employed as the inert gas. The temperature usually adopted for heating the reaction mixture is within the range of from 60°C to 120°C , preferably of from 70°C to 110°C , and the heating time is generally within
25 the period of from 30 minutes to 15 hours, preferably from

1 hour to 8 hours. No special limitation exists in the proportion of the starting 6 α -methylprednisolone to the ortho ester, but the latter is advantageously employed in molar excess. After heating, the liquid reaction mixture is treated with a weak base and taken up in an ester or alkylene halide. As the weak base, a tertiary amine such as pyridine and triethylamine as well as a weak inorganic base such as sodium carbonate, potassium carbonate and potassium bicarbonate may be used. The addition of such a weak base to the reaction mixture is effective to inhibit any decomposition of the resultant 17 α ,21-ortho ester (VI), thus serving to increase the yield of the product. Accordingly, this treatment is recommended or rather necessary in the preparation of the 17 α ,21-ortho esters. Preferred examples of the ester and alkylene halide to be mixed with the reaction mixture include ethyl acetate, methyl acetate, methylene chloride and ethylene chloride. The organic phase is then washed thoroughly with water filtered to remove any solid impurities, dried with an inert dehydrating substance such as anhydrous sodium sulfate and concentrated under atmospheric or subatmospheric pressure. All of these treatments are conducted according to conventional methods usually adopted for after-treatments of reaction products. The residue thus obtained is then crystallized from acetone-hexane. If it is difficult to

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crystallize out the product, the residue may be purified by the aid of column chromatography on silica gel impregnated with triethylamine. Usually, however, the crude product obtained as a crystalline or amorphous solid substance is used as such for the next step, o.e., the ring-opening reaction of the cyclic ortho ester.

The ring-opening reaction of the resultant cyclic 17 α ,21-ortho ester of the general formula (VI) is carried out by the aid of an acid normally in the presence of a suitable solvent, for example, a lower alkanol such as methanol. This reaction proceeds very smoothly, but usually with the formation of the 17 α -acylated compound aimed at together with a small amount of the corresponding 21-acylated compound as by-product. It is therefore recommended to adjust the acidic conditions employed to a pH range of 2 to 4 in order to obtain the desired 17 α -acylated compound selectively. Such a pH range can usually be made up by the addition of an organic acid such as oxalic acid or citric acid to the reaction system. Alternatively, a buffered solution having a pH value of 3 - 4 can be used to achieve a favourable result. It has now been surprisingly found by the present inventors that the use of a small amount of iodine (I₂) for the ring-opening reaction of the cyclic ortho ester serves to increase the yield of the desired 17 α -

acylated compound. The reaction mixture thus obtained generally contains the desired 17 α -acylated compound and a small amount of the contaminating 21-acylated compound. Column chromatography using silica gel is usually employed to eliminate the contaminant thereby obtaining the desired 17 α -acylated compound in a purer form. Alternatively, preparative thin layer chromatography using silica gel as the absorption agent may also be utilized for this purpose.

When 17 α ,21-diacylated 6 α -methylprednisolone compounds of general formula (III) are to be prepared as the end products, the 21-hydroxy group of the 17 α -acylated compounds thus obtained is acylated according to a method known per se with an acylating compound of the general formula (VII).

This acylation is advantageously carried out by using the compound of the general formula (II) and a compound of the general formula (VII) wherein X is a halogen atom or the group R³-CO-O- in the presence of a tertiary amine such as triethylamine or pyridine. This acylation is promoted very smoothly under mild conditions. When the acylating compound is used in the form of an acid anhydride, the acylation will usually be completed at ambient or room temperature within a period of from 1 to 40 hours, preferably 2-30 hours. It is possible to warm the reaction mixture slightly to accelerate the reaction thereby shortening the reaction time.

- 15 -

When the acylating compound is used in the form of an acid halide (chloride or bromide), the acylation can be carried out under milder conditions, for example, at 0°C for 20 to 40 minutes. The above acylation is normally carried out in the presence of an excess amount of a tertiary amine in an inert solvent such as methylene chloride. It is preferable to employ the acylating agent in a slightly stoichiometrical excess of the 17 α -acyl compound of the general formula (II). If the acylating compound remains unreacted in the reaction mixture, it can easily be decomposed by the addition of a lower alkanol to the reaction mixture. After completion of the reaction, the reaction mixture can be treated according to conventional methods, for example, by diluting the reaction mixture with a suitable solvent such as ethyl acetate, washing the organic phase with water sufficiently, filtering the organic phase to remove any solid impurities and then concentrated, usually under reduced pressure. The crude 17 α ,21-diacylated product thus obtained can be purified by a method known per se by recrystallization, for example, from acetone-hexane or by means of column chromatography or preparative thin layer chromatography using silica gel. It is also possible to subject a residue obtained by concentrating the reaction mixture directly to such chromatography treatment for purification.

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The new 6 α -methylprednisolone derivatives obtained by the above one- or two-step acylation processes were shown to

be 17 α -acyloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione compounds or 17 α ,21-diacyloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione compounds by subjecting the derivatives to analysis including the measurements of
 5 infra-red absorption spectra (IR), nuclear magnetic resonance spectra (NMR), mass spectra (MS) and elementary analysis.

The new 6 α -methylprednisolone derivatives of the present invention by the general formula (I) exhibit a
 10 strong local antiinflammatory activity and thus can be utilized clinically for the treatment of various dermal disorders, for example, acute or chronic eczema, contact dermatitis, eczema seborrhoicorum, atopic dermatitis, eczema infantum and psoriasis vulgaris. The new compounds
 15 of the present invention can also be utilized for treating asthma and various other allergic diseases. For the treatment of these diseases, the 6 α -methylprednisolone derivatives can be used in various types of pharmaceutical preparations, for example, ointments, creams, lotions, liquid
 20 paints, plasters and powders.

The antiinflammatory activity exhibited by the new 6 α -methyl-prednisolone derivatives is extremely good and this fact can be proved by evaluating the activity according to
 25 the vasoconstriction test. Given below is the test method for the evaluation of the pharmacological activity and results thereof.

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Test method:

From the compounds of the present invention represented by the general formula (I) and compounds for comparative tests (controls), ointments containing these compounds each in a concentration of 0.01% were prepared. These ointments were randomly applied in a definite amount (about 20mg) by a controller having no concern with the evaluation of activity onto a plastic bandage to prepare test pieces for a patch test (Finn Chamber; Epitest Ltd. Oy, Finland). Each of these test pieces was applied onto the skin in the flexor aspects of both forearms of 10 healthy adult males. After the lapse of 16 hours, all the test pieces of the plastic bandage were peeled off and the compounds remaining on the skin were gently washed off with a soap solution.

Evaluation:

The vasoconstrictive activity in terms of the degree of blanching on the skin after 2 hours and 6 hours was determined by 2 judging persons using the following four degrees:

++ (marked) + (medium) ± (slight) - (inactive)

- 18 -

according to the degree of blanching. The numerals 3, 2, 1 and 0 were arbitrarily given to the above four degrees, respectively, and the numerical data on the 10 volunteers were summed up (30.0 as the maximum value). The vasoconstrictive activity was calculated as a mean value of the results obtained by the 2 judging persons. Tables 1 and 2 show the results of this test.

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TABLE 1

Concentration a) Vasoconstrictive Activity

Compound

No

TABLE 1

No.	Compound	Concentration ^{a)} (w/w%)		Vasoconstrictive Activity	
		after 2 Hrs.		after 6 Hrs.	
1	17 α -butyryloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione	29.0		25.5	
2	11 β ,21-dihydroxy-17 α -isobutyryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione	29.0		26.0	
3	11 β ,21-dihydroxy-6 α -methyl-17 α -valeryloxy-1,4-pregnadiene-3,20-dione	21.5		18.5	
4	11 β ,21-dihydroxy-17 α -isovaleryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione	27.5		22.5	
5	17 α -benzoyloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione	26.5		23.5	
6	17 α ,21-diacetoxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione	22.5		11.0	
7	21-acetoxy-11 β -hydroxy-6 α -methyl-17 α -propionyl-oxy-1,4-pregnadiene-3,20-dione	28.0		16.0	
8	17 α -acetoxy-21-benzoyloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione	22.5		12.0	

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9	17 α -acetoxy-11 β -hydroxy-6 α -methyl-21-propionyl- oxy-1,4-pregnadiene-3,20-dione	23.0	14.5
10	21-butyryloxy-11 β -hydroxy-6 α -methyl-17 α - propionyloxy-1,4-pregnadiene-3,20-dione	25.5	13.0
11	11 β -hydroxy-21-isobutyryloxy-6 α -methyl-17 α - propionyloxy-1,4-pregnadiene-3,20-dione	24.0	13.5
12	21-benzoyloxy-11 β -hydroxy-6 α -methyl-17 α -propionyl- oxy-1,4-pregnadiene-3,20-diene	24.5	18.5
13	21-acetoxy-17 α -butyryloxy-11 β -hydroxy-6 α -methyl- 1,4-pregnadiene-3,20-dione	26.0	18.5
14	17 α -butyryloxy-11 β -hydroxy-6 α -methyl-21-propionyl- oxy-1,4-pregnadiene-3,20-dione	28.5	24.0
15	17 α ,21-dibutyryloxy-11 β -hydroxy-6 α -methyl-1,4- pregnadiene-3,20-dione	26.0	24.0
16	21-acetoxy-11 β -hydroxy-17 α -isobutyryloxy-6 α -methyl- 1,4-pregnadiene-3,20-dione	28.5	15.5
17	17 α -butyryloxy-11 β -hydroxy-21-isobutyryloxy-6 α - methyl-1,4-pregnadiene-3,20-dione	25.0	13.0
18	11 β -hydroxy-17 α -isobutyryloxy-6 α -methyl-21- propionyloxy-1,4-pregnadiene-3,20-dione	22.5	15.5
19	11 β -hydroxy-17 α ,21-diisobutyryloxy-6 α -methyl-1,4- pregnadiene-3,20-dione	17.0	13.0

20	21-acetoxy-11 β -hydroxy-6 α -methyl-17 α -valeryloxy-1,4-pregnadiene-3,20-dione	22.0	14.5
21	21-butyryloxy-11 β -hydroxy-17 α -isobutyryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione	21.0	15.5
22	11 β -hydroxy-17 α -isovaleryloxy-6 α -methyl-21-propionyloxy-1,4-pregnadiene-3,20-dione	18.5	17.0
23	11 β -hydroxy-6 α -methyl-21-propionyloxy-17 α -valeryloxy-1,4-pregnadiene-3,20-dione	19.5	15.0
24	21-acetoxy-11 β -hydroxy-17 α -isovaleryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione	24.0	19.0
<u>Controls</u>			
	hydrocortisone 21-acetate	1.0 6.0	2.5
	6 α -methylprednisolone	0.01 6.0	4.5
	betamethasone 17-valerate	0.01 25.0	22.0
	ointment base	-- 3.0	2.0
	non-treated	-- 1.5	1.0

a) Each concentration of the Compounds Nos. 1-24 is 0.01%.

b) Activity is expressed by a score for blanching degree, which correlates well to antiinflammatory activity (maximum is 30.0).

TABLE 2

No.	Compound	Concentration ^{a)} (w/w%)	Vasoconstrictive activity ^{b)} after 2 Hrs. after 6 Hrs.
1	17 α -butyryloxy-11 β -hydroxy-6 α -methyl-21-methylthioacetoxyl-1,4-pregnadiene-3,20-dione	14.5	10.5
2	11 β -hydroxy-17 α -methoxyacetoxyl-6 α -methyl-21-propionyloxy-1,4-pregnadiene-3,20-dione	16.0	8.0
3	21-butryloxy-11 β -hydroxy-17 α -methoxyacetoxyl-6 α -methyl-1,4-pregnadiene-3,20-dione	17.5	12.0
4	11 β ,21-dihydroxy-6 α -methyl-17 α -methylthioacetoxyl-1,4-pregnadiene-3,20-dione	12.5	8.0
5	11 β -hydroxy-6 α -methyl-17 α -methylthioacetoxyl-21-propionyloxy-1,4-pregnadiene-3,20-dione	23.0	18.5
6	21-butryloxy-11 β -hydroxy-6 α -methyl-17 α -methylthioacetoxyl-1,4-pregnadiene-3,20-dione	18.5	14.0
7	11 β -hydroxy-21-methoxyacetoxyl-6 α -methyl-17 α -methylthioacetoxyl-1,4-pregnadiene-3,20-dione	14.5	12.0
8	17 α -butyryloxy-11 β -hydroxy-21-methoxyacetoxyl-6 α -methyl-1,4-pregnadiene-3,20-dione	(27.0)	(21.0)

Controls

Hydrocortisone 21-acetate	1.0	4.5(6.0)	2.5(2.5)
6 α -Methylprednisolone	0.01	4.0(6.0)	3.5(4.5)
Betamethasone 17-valerate	0.01	17.0(25.0)	16.5(22.0)

a) Each concentration of the Compounds Nos. 1-8 is 0.01%.

b) Activity is expressed by a score for blanching degree which correlates well to antiinflammatory activity (maximum is 30.0). The scores showed in the parentheses of controls are employed for that of the Compound No. 8.

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As is evident from the results given in Tables 1 and 2, the compounds of the present invention possess an extremely strong vasoconstrictive activity in comparison with the starting 6-methylprednisolone. Some of the compounds of the present invention are found to be much more effective in the activity than commercially available betamethasone 17-valerate.

The present invention will now be described in more detail in the following Examples in which the new compounds of the present invention and the preparation thereof are illustrated.

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Example 1 17 α -Butyryloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione

(a) In 6 ml of dimethylformamide was dissolved 374 mg of 6 α -methylprednisolone. To this solution were added 380 mg of ethyl orthobutyrate and then 9 mg of p-toluenesulfonic acid. The mixture was heated at 80°C with stirring for 1.5 hours in a stream of argon and the reaction liquid was poured into 50 ml of ethyl acetate. To the liquid mixture were added immediately 1 ml of a 10% solution of sodium carbonate and 30 ml of water. The mixture was well shaken and the ethyl acetate phase was separated, washed twice with 30 ml of water and dried over anhydrous sodium sulfate. The solution was then filtered and the filtrate was evaporated to obtain a crude crystalline substance which was recrystallized from acetone-hexane whereby 430 mg (yield: 90.9%) of 6 α -methylprednisolone 17 α ,21-ethyl orthobutyrate was obtained as colorless needle crystals.

M.P. 154.0-166.0°C (with decomp.)

IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3340, 1720, 1645

MS m/e : 473 ($M^+ + 1$), 472 (M^+), 427, 356, 311, 297, 279, 161, 136, 135 (base peak), 121

Elementary analysis (as $\text{C}_{28}\text{H}_{40}\text{O}_6$):

Calc. (%) C 71.16; H 8.53

Found (%) C 71.03; H 8.71

In 8 ml of methanol was dissolved 400 mg of 6 α -methylprednisolone 17 α ,21-ethyl orthobutyrate. To this solution was added 1 ml of 2N-oxalic acid, and the mixture was warmed for 30 minutes at 40-45°C. The solvent was removed by distillation under reduced pressure and 80 ml of ethyl acetate was added to the residue. The ethyl acetate solution was washed twice with 30 ml of water, dried over anhydrous sodium sulfate and evaporated

under subatmospheric pressure to obtain a crude product, which was subjected to column chromatography on silica gel and fractionated with methylene chloride for purification whereby 302 mg (yield: 80.2%) of 17 α -butyryloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione was obtained.

This compound was colorless and amorphous but was confirmed to be pure in view of its physical properties and as the results of various analyses shown hereunder.

TLC (silica gel): Rf 0.51 (single spot, benzene:ethanol = 5:1)

IR $\nu_{\text{max}}^{\text{KBr}}$ cm $^{-1}$: 3400, 1720, 1710, 1650

NMR δ_{CDCl_3} : 0.80-1.20 (9H, m, -CH $_2$ CH $_3$, C $_{18}$ -CH $_3$ and C $_{6\alpha}$ -CH $_3$),
1.47 (3H, s, C $_{19}$ -CH $_3$), 4.26 (2H, br.s, C $_{21}$ -CH $_2$),
4.52 (1H, br, C $_{11}$ -CH), 6.03 (1H, s, C $_4$ -CH),
6.28 (1H, d, J=10Hz, C $_2$ -CH), 7.36 (1H, d, J=10Hz,
C $_1$ -CH)

MS m/e : 445 (M $^{+}$ + 1), 444 (M $^{+}$), 413 (M $^{+}$ - 31), 356, 327, 309,
297, 279, 161, 136 (base peak), 135, 121

Elementary analysis (as C $_{26}$ H $_{36}$ O $_6$):

Calc. (%) H 70.24 ; H 8.16

Found (%) H 70.12 ; H 8.29

(b) In 2 ml of dimethylformamide was dissolved 200 mg of 6 α -methylprednisolone. To this solution were added 180 mg of methyl orthobutyrate and 8 mg of p-toluenesulfonic acid. The mixture was heated at 110°C under a nitrogen current with stirring for one hour. To the reaction liquid were added at room temperature 1 ml of pyridine and 50 ml of ethyl acetate, and the mixture was washed twice with 30 ml of water. The ethyl acetate phase was dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product which was then

recrystallized from acetone-hexane whereby 175 mg (yield: 71.3%) of 6 α -methylprednisolone 17 α ,21-methyl orthobutyrate was obtained.

--- Next, 100 mg of this compound was dissolved in 6 ml of methanol and 0.5 ml of a buffered solution of sodium acetate was added. The mixture was stirred overnight at room temperature and the reaction liquid was treated in the same manner as described in the foregoing (a) to obtain a crude product which was subjected to preparative thin layer chromatography on silica gel for purification whereby 71 mg (yield: 72.8%) of 17 α -butyryloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione was obtained. This compound was in agreement in physical properties and analytical data with that obtained in the above (a).

Example 2 11 β ,21-Dihydroxy-17 α -isobutyryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione

(a) In 6 ml of dimethylformamide was dissolved 750 mg of 6 α -methylprednisolone. To this solution were added 890 mg of methyl orthobutyrate and then 34 mg of p-toluenesulfonic acid. The mixture was heated at 80°C with stirring in a stream of argon for one hour and then 80 ml of ethyl acetate was poured into the reaction liquid. Then, 2 ml of a 10% solution of sodium carbonate was immediately added to the reaction liquid, and 50 ml of water was added thereto. The liquid mixture was well shaken and the ethyl acetate layer was separated, washed with water and dried over anhydrous sodium sulfate. The ethyl acetate was distilled off and the resultant crude crystalline product was recrystallized whereby 862 mg (yield: 93.9%) of 6 α -methylprednisolone 17 α ,21-methyl orthoisobutyrate was obtained as colorless needle crystals (m.p. 172.0-175.0°C with decomp.).

Analytical data of this compound were as follows:

IR_{max}^{KBr} cm⁻¹ : 3320 (OH), 1715 (C=O), 1645 (C=O)

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MS m/e : 459 ($M^+ + 1$), 458 (M^+), 427 ($M^+ - 31$), 325, 297, 279,
161, 136 (base peak), 135, 121

Elementary analysis (as $C_{27}H_{38}O_6$)

Calc. (%) C 70.71 ; H 8.35

5 Found (%) C 70.58 ; H 8.41

In 20 ml of methanol was dissolved 460 mg of the thus
obtained 6 α -methylprednisolone 17 α ,21-methyl orthoisobutyrate.
To this solution was added 1 ml of 2N-oxalic acid, and the
mixture was warmed at 40-50°C for 10 minutes. The solvent was
10 distilled off under reduced pressure and 50 ml of ethyl acetate
was added to the residue. The ethyl acetate solution was washed
with water and dried over anhydrous sodium sulfate, and the
solvent was removed by distillation under reduced pressure to
obtain a crystalline residue which was then subjected to column
15 chromatography on silica gel, eluted and fractionated with
methylene chloride whereby 344 mg (yield: 77.3%) of 11 β ,21-
dihydroxy-17 α -isobutyryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione
was obtained. This compound was a colorless amorphous substance
but was confirmed to be pure in view of the following physical
20 properties and spectra:

TLC (silica gel): Rf 0.52 (single spot, benzene : ethanol = 4:1)

IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400 (OH), 1720 (C=O), 1710 (C=O), 1650 (C=O)

NMR δ_{CDCl_3} : 0.95 (3H, s, C_{18} -CH₃), 1.15 (6H, d, -CH $\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$),
1.15 (3H, d, $C_{6\alpha}$ -CH₃), 1.47 (3H, s, C_{19} -CH₃),
25 4.23 (2H, s, C_{21} -CH₂), 4.50 (1H, br, C_{11} -CH),
6.05 (1H, s, C_4 -CH), 6.28 (1H, d, J=10 Hz, C_2 -CH),
7.30 (1H, d, J=10 Hz, C_1 -CH)

MS m/e : 445 ($M^+ + 1$), 444 (M^+), 413 ($M^+ - 31$), 358, 297, 279, 161,
30 136, 135 (base peak), 121

Elementary analysis (as $C_{26}H_{36}O_6$)

Calc. (%) C 70.24 ; H 8.16

Found (%) C 70.28 ; H 8.31

(b) To 3 ml of methylene chloride was added 100 mg of 6 α -methylprednisolone 17 α ,21-methyl orthoisobutyrate obtained in the foregoing (a). To this mixture was added under agitation 5 mg of iodine, and the reaction was allowed to proceed at room temperature for 30 minutes. The reaction liquid was then concentrated under reduced pressure and the resultant crude product was subjected to preparative thin layer chromatography (silica gel) whereby 82 mg of 11 β ,21-dihydroxy-17 α -isobutyryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione was obtained. This compound was in agreement in physical properties and spectrum data in IR, NMR and MS with the title compound obtained in the preceding (a).

Example 3 11 β ,21-Dihydroxy-6 α -methyl-17 α -valeryloxy-1,4-pregnadiene-3,20-dione

In 3 ml of dimethylformamide was dissolved 374 mg of 6 α -methylprednisolone. To this solution were added 324 mg of methyl orthovalerate and then 17 mg of p-toluenesulfonic acid. The mixture was heated at 90°C with stirring under an argon current for 5 hours. To the reaction liquid were then added at room temperature 50 ml of ethyl acetate and 0.5 ml of a 10% aqueous solution of sodium carbonate. To this mixture was further added 30 ml of water, and the whole was well shaken. The ethyl acetate layer was separated, washed twice with 30 ml of water and then dried over anhydrous sodium sulfate. The ethyl acetate solution was filtered and the filtrate was concentrated to obtain a crude product which was then subjected to a separation treatment using column chromatography on silica gel impregnated

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with triethylamine whereby 433 mg (yield: 91.7%) of 6 α -methyl-prednisolone 17 α ,21-methyl orthovalerate was obtained as a colorless amorphous solid. Shown below are various analytical data of this compound.

IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400 (OH), 1720 (C=O), 1645 (C=O)

MS m/e : 473 ($M^+ + 1$), 472 (M^+), 441, 356, 297, 279, 161, 136, 135 (base peak), 121, 85

Elementary analysis (as $\text{C}_{28}\text{H}_{40}\text{O}_6$)

Calc. (%) C 71.16 ; H 8.53

Found (%) C 71.23 ; H 8.69

In 8 ml of methanol was dissolved 236 mg of the 6 α -methyl-prednisolone 17 α ,21-methyl orthovalerate thus obtained, and the solution was warmed at 40°C. To the solution was added 0.5 ml of 2N-oxalic acid, and the mixture was warmed with stirring for 10 minutes. The solvent was then distilled off under reduced pressure and the resultant residue was subjected to preparative thin layer chromatography whereby 187 mg (yield: 81.7%) of 11 β ,21-dihydroxy-6 α -methyl-17 α -valeryloxy-1,4-pregnadiene-3,20-dione was obtained as a colorless amorphous solid. The structure of this compound was confirmed by the following physical properties and results of various analyses:

TLC : R f 0.53 (silica gel, single spot, benzene : ethanol = 4:1)

IR $\nu_{\text{max}}^{\text{KBr}}$ cm^{-1} : 3400 (OH), 1720 (C=O), 1715 (C=O), 1655 (C=O)

NMR δ ppm (CDCl_3) : 0.95 (3H, s, C_{18} -CH $_3$), 0.88-1.25 (3H, m, $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.11 (3H, d, $J=6\text{Hz}$, $\text{C}_{6\alpha}$ -CH $_3$), 1.52 (3H, s, C_{19} -CH $_3$), 4.28 (2H, s, C_{21} -CH $_2$), 4.52 (1H, br, C_{11} -CH), 6.02 (1H, br.s, C_4 -CH), 6.24 (1H, d, $J=10\text{ Hz}$, C_2 -CH), 7.38 (1H, d, $J=10\text{ Hz}$, C_1 -CH)

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MS m/e : 459 ($M^+ + 1$), 458 (M^+), 441, 440, 427, 356, 327, 325,
297, 281, 279, 161, 136 (base peak), 135, 121, 85

Elementary analysis (as $C_{27}H_{38}O_6$)

Calc. (%) C 70.72 ; H 8.35

Found (%) C 70.59 ; H 8.53

Example 4 11 β ,21-Dihydroxy-17 α -isovaleryloxy-6 α -methyl-1,4-
pregnadiene-3,20-dione

In 6 ml of dimethylformamide was dissolved 749 mg of 6 α -
methylprednisolone. To this solution were added 973 mg of
methyl orthoisovalerate and 34 mg of p-toluenesulfonic acid,
and the mixture was heated at 80°C with stirring under an argon
current for one hour. To the reaction liquid were then added
at room temperature 80 ml of ethyl acetate, 0.5 ml of a 10%
solution of sodium carbonate and 30 ml of water, and the mixture
was well shaken. The ethyl acetate layer was separated, washed
twice with 30 ml of water and dried over anhydrous sodium sulfate.
The ethyl acetate solution was filtered and the filtrate was
concentrated to obtain a crude product which was then recryst-
tallized from benzene-hexane whereby 783 mg (yield: 82.8%) of
6 α -methylprednisolone 17 α ,21-methyl orthoisovalerate was obtained
as colorless needle crystals.
M.P. 168.0-171.0°C (with decomp.)

IR ν_{max}^{KBr} cm^{-1} : 3400, 1715, 1650

MS m/e : 473 ($M^+ + 1$), 472 (M^+), 441 ($M^+ - 31$), 356, 297, 161, 136,
135 (base peak), 121

Elementary analysis (as $C_{28}H_{40}O_6$)

Calc. (%) C 71.16 ; H 8.53

Found (%) C 71.01 ; H 8.41

In 20 ml of methanol was dissolved 720 mg of 6 α -methyl-

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prednisolone 17 α ,21-methyl orthoisovalerate. To the solution was added 2 ml of 2N-oxalic acid, and the mixture was warmed at 40°C for 15 minutes. The solvent was then distilled off and 80 ml of ethyl acetate was added to the residue. The ethyl acetate phase was washed with 1 ml of a 10% solution of sodium carbonate and 30 ml of water, dried over anhydrous sodium sulfate and concentrated to obtain a crude product which was then subjected to column chromatography on silica gel whereby 486 mg (yield: 69.5%) of 11 β ,21-dihydroxy-17 α -isovaleryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione was obtained. This compound was colorless and amorphous but was confirmed to be pure in view of the its physical properties and various analytical data shown below.

TLC (silica gel) : Rf 0.53 (single spot, benzene : ethanol= 4:1)

IR ν_{max} KBr cm^{-1} : 3400, 1720, 1710, 1650

NMR δ CDCl₃ : 0.90 (3H, s, C₁₈-CH₃), 0.96 (6H, s, CH₂CH $\begin{smallmatrix} \text{CH}_3 \\ \text{CH}_3 \end{smallmatrix}$), 1.11 (3H, d, J=6 Hz, C_{6 α} -CH₃), 1.97 (3H, s, C₁₉-CH₃), 4.30 (2H, s, C₂₁-CH₂), 4.50 (1H, br, C₁₁-CH), 6.02 (1H, s, C₄-CH), 6.27 (1H, d, J=10 Hz, C₂-CH), 7.32 (1H, d, J=10 Hz, C₁-CH)

MS m/e : 459 (M⁺+1), 458 (M⁺), 440 (M⁺-18), 427 (M⁺-31), 356, 338, 327, 325, 281, 161, 136 (base peak), 135, 121

Elementary analysis (as C₂₇H₃₈O₆)

Calc. (%) C 70.71 H 8.35

Found (%) C 70.62 H 8.57

Example 5 17 α -benzoyloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione

A mixture of 2.0 g of 6 α -methylprednisolone, 2.0 g of methyl orthobenzoate, 8 ml of dimethylformamide and 0.09 g of p-toluene-

sulfonic acid was heated at 80°C with stirring under an argon current for 5 hours. To this reaction liquid were then added at room temperature 4 ml of a 10% aqueous solution of sodium carbonate, 40 ml of water and 100 ml of ethyl acetate, and the mixture was shaken. The ethyl acetate layer was separated, washed with water, dried over anhydrous sodium carbonate and filtered. The filtrate was concentrated under reduced pressure and the resultant crude product was subjected to column chromatography on silica gel impregnated with triethylamine and eluted with methylene chloride whereby 1.75 g (yield: 65.4%) of 6 α -methylprednisolone 17 α ,21-methyl orthobenzoate was obtained, which showed a single spot in TLC (silica gel).

Although this compound was a colorless amorphous substance, it was identified by the following IR-absorption and mass spectral data and the result of elementary analysis:

IR_{max}^{KBr} cm⁻¹ : 3350 (OH), 1715 (C=O), 1645 (C=O)

MS m/e : 493 (M⁺+1), 492 (M⁺), 475, 461 (M⁺-31), 356, 297, 279, 161, 136, 135, 105 (base peak), 77

Elementary analysis (as C₃₀H₃₆O₆)

Calc. (%) C 73.14 ; H 7.37

Found (%) C 73.02 ; H 7.49

In 30 ml of methanol was dissolved 1.5 g of the 6 α -methylprednisolone 17 α ,21-methyl orthobenzoate thus obtained. To this solution was added 15 ml of a sodium acetate buffered solution, and the mixture was warmed at 40°C for 10 minutes. The solvent was distilled off under reduced pressure and the resulting residue was subjected to preparative thin layer chromatography (silica gel) whereby 1.17 g (yield: 80.8%) of 17 α -benzoyloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione was obtained as a colorless amorphous substance. The physical properties and

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spectral data of this compounds are as follows:

TLC (silica gel) : Rf 0.53 (single spot, benzene:ethanol = 4:1)

IR ν_{max} ^{KBr} cm⁻¹ : 3400 (OH), 1710 (C=O), 1705 (C=O), 1650 (C=O)

NMR δ CDCl₃ : 1.04 (3H, s, C₁₈-CH₃), 1.14 (3H, d, C_{6 α} -CH₃),
 1.48 (3H, s, C₁₉-CH₃), 4.32 (2H, s, C₂₁-CH₂),
 4.57 (1H, br, C₁₁-CH), 6.06 (1H, s, C₄-CH), 6.30
 (1H, d, J=10Hz, C₂-CH), 7.35 (1H, d, J=10Hz, C₁-CH),
 7.40-8.10 (5H, m, Ph)

MS m/e : 479 (M⁺+1), 478 (M⁺), 447 (M⁺-31), 327, 309, 297, 281,
 161, 136, 135, 122, 105 (base peak), 77

Elementary analysis (as C₂₉H₃₄O₆)

Calc. (%) C 72.78 ; H 7.16

Found (%) C 72.89 ; H 7.33

Example 6 17 α ,21-diacetoxy-11 β -hydroxy-6 α -methyl-1,4-
 pregnadiene-3,20-dione

To 3 ml of dimethylformamide was dissolved 749 mg of 6 α -methylprednisolone. To this solution were added 649 mg of ethyl orthoacetate and 17 mg of p-toluenesulfonic acid, and the mixture was heated at 75°C with stirring for 1.5 hours. To the reaction liquid were then added at room temperature successively 80 ml of ethyl acetate, 0.5 ml of a 10% solution of sodium carbonate and 30 ml of water, and the mixture was shaken. The ethyl acetate layer was separated, washed twice with 30 ml of water, dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to obtain a crude product as a crystalline solid, which was recrystallized from acetone-hexane whereby 822 mg (yield: 92.5%) of 6 α -methylprednisolone 17 α ,21-ethyl orthoacetate was obtained as colorless needle crystals.

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M.P. 134.0-136.0°C (with decomp.)

IR_{max}^{KBr} cm⁻¹ : 3440, 1715, 1650

MS m/e : 445 (M⁺+1), 444 (M⁺), 399, 356, 297, 279, 237, 161,
136, 135 (base peak), 121

5 Elementary analysis (as C₂₆H₃₆O₆)

Calc. (%) C 70.24 ; H 8.16

Found (%) C 70.13 ; H 8.08

10 In 8 ml of methanol was dissolved 270 mg of 6 α -methyl-
prednisolone 17 α ,21-ethyl orthoacetate. To this solution was
added 1.5 ml of 2N-oxalic acid, and the mixture was heated at
40°C for 10 minutes. The reaction liquid was concentrated
and the resultant residue was well shaken with 50 ml of ethyl
acetate, 1 ml of a 10% solution of sodium carbonate and 30 ml
15 of water. The ethyl acetate layer was separated, washed twice
with 30 ml of water, dried over anhydrous sodium sulfate and
filtered. The filtrate was concentrated to obtain a crude
product which was then subjected to preparative thin layer
chromatography on silica gel whereby 177 mg (yield: 69.8%) of
17 α -acetoxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-
20 dione was obtained.

25 In 3 ml of methylene chloride was dissolved 114 mg of the
thus obtained 17 α -acetyl compound. To this solution were added
56 mg of acetic anhydride and 101 mg of triethylamine and the
mixture was stirred at room temperature for 8 hours. To the
solution was added 1 ml of dry methanol, and the mixture was
allowed to stand overnight and concentrated under reduced pressure.
The resultant residue was purified by subjecting it directly to
preparative thin layer chromatography (silica gel) and then
recrystallized from acetone-hexane whereby 105 mg (yield: 83.3%)

of 17 α ,21-diacetoxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione was obtained as colorless fine needle crystals. Below are physical properties and various analytical data of this compound.

5 M.P. 221.0-224.0°C

TLC (silica gel): R_f 0.37 (single spot, benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3380, 1755, 1730, 1650

10 NMR δ CDCl₃ : 1.03 (3H, s, C₁₈ -CH₃), 1.13 (3H, d, J=7.0Hz, C_{6 α} -CH₃), 1.47 (3H, s, C₁₉ -CH₃), 2.05 (3H, s, C₁₇ -COCH₃), 2.17 (3H, s, C₂₁ -COCH₃), 4.47 (1H, br, C₁₁ -CH), 4.81 (2H, d, J=4.5Hz, C₂₁ -CH₂), 6.01 (1H, s, C₄ -CH), 6.25 (1H, d, J=10Hz, C₂ -CH), 7.27 (1H, d, J=10Hz, C₁ -CH)

15 MS m/e : 459 (M⁺+1), 458 (M⁺), 441, 440 (M⁺-18), 338, 356, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 43

Elementary analysis (as C₂₆H₃₄O₇)

Calc. (%) C 68.10 ; H 7.47

Found (%) C 67.91 ; H 7.21

20 Example 7 21-Acetoxy-11 β -hydroxy-6 α -methyl-17 α -propionyloxy-1,4-pregnadiene-3,20-dione

25 In 4 ml of dimethylformamide was dissolved 1.12 g of 6 α -methylprednisolone. To this solution were added 1.06 g of ethyl orthopropionate and 0.026 g of p-toluenesulfonic acid, and the mixture was heated with stirring under an argon current at 80°C for 1.5 hours. Next, 100 ml of ethyl acetate and 0.5 ml of a 10% aqueous solution of sodium carbonate were added to the reaction liquid at room temperature and then 50 ml of water was also added thereto. This mixture was well shaken and the ethyl acetate layer was separated, washed twice with 30 ml of water and dried over

anhydrous sodium sulfate. After filtration, the filtrate was concentrated and the resultant crude product was recrystallized from ether whereby 1.28 g (yield: 92.8%) of 6 α -methylprednisolone 17 α ,21-ethyl orthopropionate was obtained as colorless needle crystals. Below are physical properties and various analytical data of this compound.

M.P. 160.0 - 164.0°C (with decomp.)

IR_{max}^{KBr} cm⁻¹ : 3350 (OH), 1720 (C=O), 1645 (C=O)

MS m/e : 459 (M⁺+1), 458 (M⁺), 441, 430, 413, 395, 356, 311, 297, 279, 237, 161, 136, 135 (base peak), 121, 57

Elementary analysis (as C₂₇H₃₈O₆)

Calc. (%) C 70.71 ; H 8.35

Found (%) C 70.59 ; H 8.47

In 8 ml of methanol was dissolved 320 mg of the 6 α -methylprednisolone 17 α ,21-ethyl orthopropionate. To this solution was added 1.5 ml of 2N-oxalic acid, and the mixture was heated at 40°C for 10 minutes. The resultant reaction liquid was concentrated under reduced pressure. To the residue were added successively 50 ml of ethyl acetate, 0.5 ml of a 10% solution of sodium carbonate and 30 ml of water, and the mixture was well shaken. The ethyl acetate layer was separated, dried over anhydrous sodium sulfate and concentrated to obtain a crude product which was then subjected to preparative thin layer chromatography on silica gel whereby 235 mg (yield: 78.3%) of 11 β ,21-dihydroxy-6 α -methyl-17 α -propionyloxy-1,4-pregnadiene-3,20-dione was obtained.

In 4 ml of methylene chloride was dissolved 210 mg of this compound. To this solution were added 400 mg of triethylamine and 120 mg of acetic anhydride, and the mixture was stirred for

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7 hours at room temperature. To this reaction liquid was then added 1 ml of methanol, and the mixture was stirred for further 2 hours and then concentrated under reduced pressure. The resultant residue was directly subjected to preparative thin layer chromatography (silica gel) for purification and then recrystallized from ether to obtain 107 mg (yield: 80.6%) of the title compound as colorless fine needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 129.0 - 131.0°C

TLC (silica gel) : Rf 0.37 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3380, 1755, 1730, 1650

¹H NMR δCDCl₃ : 1.06 (3H, s, C₁₈-CH₃), 1.15 (3H, d, J=6.0Hz, C_{6α}-CH₃), 1.12 (3H, t, J=8Hz, CH₂CH₃), 1.48 (3H, s, C₁₉-CH₃), 2.18 (3H, s, COCH₃), 4.52 (1H, br, C₁₁-CH), 4.80 (2H, d, J=4.0Hz, C₂₁-CH₂), 6.05 (1H, s, C₄-CH), 6.28 (1H, d, J=10Hz, C₂-CH), 7.33 (1H, d, J=10Hz, C₁-CH)

MS m/e : 473 (M⁺+1), 472 (M⁺), 455, 454, 418, 401, 398, 327, 325, 299, 297, 281, 279, 185, 161, 136, 135, 121, 91, 57 (base peak), 43

Elementary analysis (as C₂₇H₃₆O₇)

Calc. (%) C 68.62 ; H 7.68

Found (%) C 68.42 ; H 7.42

Example 8 17α-Acetoxy-21-benzoyloxy-11β-hydroxy-6α-methyl-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 208 mg of 17α-acetoxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method described in Example 6. To this solution was added 202 mg of triethylamine, and the mixture

was ice-cooled. Next, 140 mg of benzoyl chloride was directly added to the solution and the mixture was stirred for one hour. To the solution was further added 1 ml of methanol, and the mixture was stirred for one hour. The reaction liquid was concentrated under reduced pressure and the resultant residue was directly subjected to preparative thin layer chromatography (silica gel) for purification whereby 204 mg (yield: 78.5%) of the title compound was obtained as a colorless amorphous solid. The structure of this compound was confirmed by the following physical properties and results of various analyses:

M.P. 135.5 - 138.5°C (as reference)

TLC (silica gel) : R_f 0.41 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3400, 1735, 1720, 1650

NMRδCDCl₃ : 1.07 (3H, s, C₁₈-CH₃), 1.12 (3H, d, J=6Hz, C_{6α}-CH₃), 1.46 (3H, s, C₁₉-CH₃), 2.08 (3H, s, COCH₃), 4.52 (1H, br, C₁₁-CH), 5.00 (2H, d, J=4.0Hz, C₂₁-CH₂), 6.00 (1H, s, C₄-CH), 6.26 (1H, d, J=10Hz, C₂-CH), 7.26 (1H, d, J=10Hz, C₁-CH), 7.30-8.25 (5H, m, Ph)

MS m/e : 521 (M⁺+1), 520 (M⁺), 503, 502, 460, 413, 385, 325, 297, 279, 239, 161, 136, 135, 121, 105 (base peak), 77, 43

Elementary analysis (as C₃₁H₃₆O₇)

Calc. (%) C 71.52 ; H 6.97

Found (%) C 71.72 ; H 7.26

Example 9 17α-Acetoxy-11β-hydroxy-6α-methyl-21-propionyloxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 178 mg of 17α-acetoxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method described in Example 6. To

this solution was added 395 mg of propionic anhydride and 480 mg of pyridine, and the mixture was stirred for 19 hours at room temperature. The reaction liquid was treated as described in Example 6 whereupon 170 mg (yield: 85.0%) of the title compound was obtained as colorless needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 161.5 - 163.5°C

TLC (silica gel) : Rf 0.38 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3360, 1740, 1725, 1715, 1650

NMRδCDCl₃ : 0.89-1.27 (9H, m, -CH₂CH₃, C₁₈-CH₃ and C_{6α}-CH₃), 1.45 (3H, s, C₁₉-CH₃), 2.02 (3H, s, -COCH₃), 4.50 (1H, br, C₁₁-CH), 4.77 (2H, d, J=6Hz, C₂₁-CH₂), 6.07 (1H, s, C₄-CH), 6.31 (1H, d, J=10Hz, C₂-CH), 7.37 (1H, d, J=10Hz, C₁-CH)

MS m/e : 473 (M⁺+1), 472 (M⁺), 455, 454, 412, 346, 337, 325, 297, 279, 189, 161, 136 (base peak), 135, 121

Elementary analysis (as C₂₇H₃₆O₇)

Calc. (%) C 68.62 ; H 7.68

Found (%) C 68.57 ; H 7.73

Example 10 21-Butyryloxy-11β-hydroxy-6α-methyl-17α-propionyloxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 215 mg of 11β,21-dihydroxy-6α-methyl-17α-propionyloxy-1,4-pregnadiene-3,20-dione obtained according to the method described in Example 7. To this solution were added 404 mg of triethylamine and 316 mg of butyric anhydride, and the mixture was stirred for 18 hours at room temperature. Next, 2 ml of methanol was added to this reaction liquid and the mixture was stirred for further 4 hours. The reaction liquid was concentrated under reduced pressure and

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the obtained residue was directly subjected to preparative thin layer chromatography (silica gel) for purification and then recrystallized from ether-hexane whereby 203 mg (yield: 81.2%) of the title compound was obtained as colorless platelet crystals.

5 Shown below are physical properties and various analytical data of this compound.

M.P. 112.5 - 114.5°C

TLC (silica gel) : Rf 0.40 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3400, 1740, 1730, 1720, 1650

10 NMRδCDCl₃ : 0.98-1.23 (9H, m, CH₂CH₂CH₃, CH₂CH₃ and C_{6α}-CH₃),
1.05 (3H, s, C₁₈-CH₃), 1.47 (3H, s, C₁₉-CH₃), 4.51
(1H, br, C₁₁-CH), 4.77 (2H, d, J=5.0Hz, C₂₁-CH₂),
6.02 (1H, s, C₄-CH), 6.27 (1H, d, J=10Hz, C₂-CH),
7.28 (1H, d, J=10Hz, C₁-CH)

15 MS m/e : 501 (M⁺+1), 500 (M⁺), 483, 482, 426, 411, 365, 356,
338, 325, 297, 279, 189, 187, 161, 136 (base peak),
135, 121, 91, 71, 57

Elementary analysis (as C₂₉H₄₀O₇)

Calc. (%) C 69.57 ; H 8.05

20 Found (%) C 69.59 ; H 7.82

Example 11 11β-Hydroxy-21-isobutyryloxy-6α-methyl-17α-propionyloxy-1,4-pregnadiene-3,20-dione

25 In 4 ml of methylene chloride was dissolved 215 mg of 11β,21-dihydroxy-6α-methyl-17α-propionyloxy-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 7. To this solution were added 348 mg of diethylmethylanine and 316 mg of isobutyric anhydride, and the mixture was stirred for 18 hours at room temperature. Next, 2 ml of methanol was added to the mixture and the whole was stirred for 3 hours. The

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reaction liquid was concentrated under reduced pressure and the obtained residue was purified by subjecting it directly to preparative thin layer chromatography (silica gel) and recrystallized from ether-hexane whereby 216 mg (yield: 86.4%) of the title compound was obtained as colorless needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 144.0 - 146.0°C

TLC (silica gel): Rf 0.41 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3360, 1740, 1730, 1650

NMRδCDCl₃: 1.06 (3H, s, C₁₈-CH₃), 1.25 (6H, d, J=6Hz,

$-\text{CH} \begin{array}{l} \text{CH}_3 \\ \text{CH}_3 \end{array}$), 0.97-1.20 (6H, m, CH₂CH₃ and C_{6α}-CH₃),

1.47 (3H, s, C₁₉-CH₃), 4.46 (1H, br, C₁₁-CH), 4.76

(2H, d, J=6Hz, C₂₁-CH₂), 6.04 (1H, s, C₄-CH), 6.27

(1H, d, J=10Hz, C₂-CH), 7.28 (1H, d, J=10Hz, C₁-CH)

MS m/e: 501 (M⁺+1), 500 (M⁺), 483, 482, 426, 411, 365, 356,

325, 297, 279, 189, 187, 161, 136 (base peak), 135

121, 91, 71, 57

Elementary analysis (as C₂₉H₄₀O₇)

Calc. (%): C 69.57 ; H 8.05

Found (%): C 69.63 ; H 8.16

Example 12 21-Benzoyloxy-11β-hydroxy-6α-methyl-17α-propionyloxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 235 mg of 11β,21-dihydroxy-6α-methyl-17α-propionyloxy-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 7. To this solution were added 120 mg of benzoyl chloride and 133 mg of pyridine, and the mixture was stirred for 22 hours at room

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temperature. The reaction liquid was then treated in the same manner as described in Example 8 whereupon 246 mg (yield: 84.3%) of the title compound was obtained. This compound was a colorless amorphous solid but was confirmed to be pure in view of its physical properties and results of various analyses shown below.

TLC (silica gel): Rf 0.43 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3400, 1730, 1720, 1700, 1650

NMR δ CDCl₃ : 1.00-1.23 (9H, m, -CH₂CH₃, C₁₈-CH₃ and C_{6 α} -CH₃),
1.45 (3H, s, C₁₉-CH₃), 4.48 (1H, br, C₁₁-CH), 5.00
(2H, d, J=5Hz, C₂₁-CH₂), 6.05 (1H, s, C₄-CH), 6.28
(1H, d, J=10Hz, C₂-CH), 7.23-8.18 (6H, m, C₁-CH
and Ph)

MS m/e : 535 (M⁺+1), 534 (M⁺), 516, 460, 399, 325, 297, 279
161, 136, 135, 121, 106, 105 (base peak), 77

Elementary analysis (as C₃₂H₃₈O₇)

Calc. (%): C 71.89 ; H 7.16

Found (%): C 71.72 ; H 7.30

Example 13 21-Acetoxy-17 α -butyryloxy-11 β -hydroxy-6 α -methyl-
1,4-pregnadiene-3,20-dione

In 2 ml of methylene chloride was dissolved 65 mg of 17 α -butyryloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 1-(a). To this solution were dissolved 0.2 ml of pyridine and 0.2 ml of acetic anhydride, and the mixture was stirred for 6 hours at room temperature. To the mixture was added 2 ml of methanol, and the whole was stirred for further 2 hours. Ethyl acetate (50 ml) was added to the reaction liquid and the mixture was treated in the same manner as described in Example 6 whereupon 56 mg (yield: 78.9%) of the title compound was obtained as

colorless fine needle crystals. Shown below are physical properties and various analytical data of this compounds.

M.P. 158.5 - 160.5°C

TLC (silica gel): R_f 0.38 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3380, 1755, 1725, 1720, 1650

NMR δ CDCl₃ : 0.96 (3H, t, J=7Hz, CH₂CH₂CH₃), 1.06 (3H, s, C₁₈-CH₃), 1.15 (3H, d, J=6Hz, C_{6 α} -CH₃), 1.48 (3H, s, C₁₉-CH₃), 2.19 (3H, s, COCH₃), 4.48 (1H, br, C₁₁-CH), 4.79 (2H, d, J=4Hz, C₂₁-CH₂), 6.03 (1H, s, C₄-CH), 6.26 (1H, d, J=10Hz, C₂-CH), 7.31 (1H, d, J=10Hz, C₁-CH)

MS m/e : 487 (M⁺+1), 486 (M⁺), 469, 398, 383, 356, 325, 297, 279, 263, 189, 161, 136 (base peak), 135, 121, 91, 71, 43

Elementary analysis (as C₂₈H₃₈O₇)

Calc. (%): C 69.12 ; H 7.87

Found (%): C 68.83 ; H 7.95

Example 14 17 α -Butyryloxy-11 β -hydroxy-6 α -methyl-21-propionyloxy-1,4-pregnadiene-3,20-dione

In 2 ml of methylene chloride was dissolved 145 mg of 17 α -butyryloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 1-(a). To this solution were added 210 mg of pyridine and 150 mg of propionic anhydride, and the mixture was stirred for 24 hours at room temperature. To this reaction liquid was added 50 ml of ethyl acetate, and the liquid mixture was washed successively with 30 ml of water, 10 ml of a 1% solution of sodium carbonate, 30 ml of water, 10 ml of 1% hydrochloric acid and twice 30 ml of water and then dried over anhydrous sodium sulfate. The

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mixture was filtered and the filtrate was concentrated to obtain a crude product which was then purified by means of preparative thin layer chromatography (silica gel) and recrystallized from acetone-hexane whereby 145 mg (yield: 88.8%) of the title compound was obtained as colorless needle crystals.

M.P. 121.0 - 122.5°C

TLC (silica gel): Rf 0.41 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3400, 1740, 1720, 1715, 1650

NMR δ CDCl₃: 1.02 (6H, t, J=7Hz, CH₂CH₃x2), 1.02 (3H, s, C₁₈-CH₃),
1.18 (3H, d, J=6Hz, C₆ α -CH₃), 1.44 (3H, s, C₁₉-CH₃),
4.48 (1H, br, C₁₁-CH), 4.73 (2H, d, J=5Hz, C₂₁-CH₂),
6.00 (1H, s, C₄-CH), 6.24 (1H, d, J=10Hz, C₂-CH),
7.30 (1H, d, J=10Hz, C₁-CH)

MS m/e: 501 (M⁺+1), 500 (M⁺), 482, 413, 325, 297, 279, 161,
136 (base peak), 135, 121

Elementary analysis (as C₂₉H₄₀O₇)

Calc. (%): C 69.57 ; H 8.05

Found (%): C 69.71 ; H 8.16

Example 15 17 α ,21-Dibutyryloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione

In 2 ml of methylene chloride was dissolved 105 mg of 17 α -butyryloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 1-(a). To this solution were added 187 mg of butyric anhydride and 186 mg of pyridine, and the mixture was stirred for 24 hours at room temperature. To this reaction liquid was added 50 ml of ethyl acetate, and the ethyl acetate solution was washed successively with 30 ml of water, 2 ml of a 10% solution of sodium carbonate, 30 ml of water, 2 ml of 10% hydrochloric acid

and twice 30 ml of water and dried over anhydrous sodium sulfate. The solution was filtered and the filtrate was concentrated to obtain a crude product which was then subjected to preparative thin layer chromatography (silica gel) for purification and then recrystallized from acetone-hexane whereby 115 mg (yield: 95.4%) of the title compound was obtained as colorless needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 142.0 - 144.0°C

TLC (silica gel): R_f 0.42 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3380, 1740, 1725, 1715, 1650

NMRδCDCl₃: 0.97 (3H, s, C₁₈-CH₃), 1.07 (6H, s, -CH₂CH₃×2), 1.15 (3H, d, J=6Hz, C_{6α}-CH₃), 1.48 (3H, s, C₁₉-CH₃), 4.53 (1H, br, C₁₁-CH), 4.80 (2H, d, J=5Hz, C₂₁-CH₂), 6.09 (1H, s, C₄-CH), 6.32 (1H, d, J=10Hz, C₂-CH), 7.34 (1H, d, J=10Hz, C₁-CH)

MS m/e: 515 (M⁺+1), 514 (M⁺), 496, 427, 297, 279, 161, 136, 135, 121, 71 (base peak)

Elementary analysis (as C₃₀H₄₂O₇)

Calc. (%): C 70.01 ; H 8.23

Found (%): C 70.18 ; H 8.43

Example 16 21-Acetoxy-11β-hydroxy-17α-isobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 180 mg of 11β,21-dihydroxy-17α-isobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 2-(a). To this solution were added 200 mg of triethylamine and 102 mg of acetic anhydride, and the mixture was stirred for 7 hours at room temperature. To the reaction liquid

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was added 2 ml of methanol, and the mixture was stirred for further 2 hours and then concentrated under reduced pressure. The resultant residue was subjected to preparative thin layer chromatography (silica gel) for purification and then recrystallized from ether-hexane whereby 158 mg (yield: 81.0%) of the title compound was obtained as colorless platelet crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 141.5 - 143.5°C

TLC (silica gel): Rf 0.39 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3350, 1750, 1730, 1725, 1650

NMRδCDCl₃: 1.03 (3H, s, C₁₈-CH₃), 1.10 (3H, m, C_{6α}-CH₃),
1.13 (6H, d, J=8Hz, -CH₂-CH₃), 1.43 (3H, s, C₁₉-CH₃),

2.17 (3H, s, COCH₃), 4.50 (1H, br, C₁₁-CH), 4.77 (2H,

d, J=5Hz, C₂₁-CH₂), 6.06 (1H, s, C₄-CH), 6.28 (1H,

d, J=10Hz, C₂-CH), 7.26 (1H, d, J=10Hz, C₁-CH)

MS m/e: 487 (M⁺+1), 486 (M⁺), 469, 468, 413, 398, 351, 325,
297, 279, 263, 161, 136, 135, 121, 91, 71, 43 (base
peak)

Elementary analysis (as C₂₈H₃₈O₇)

Calc. (%): C 69.11 ; H 7.87

Found (%): C 68.91 ; H 8.00

Example 17 17α-Butyryloxy-11β-hydroxy-21-isobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 160 mg of 17α-butyryloxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 1-(a). To this solution were added 171 mg of isobutyric

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anhydride and 174 mg of diethylmethylamine, and the mixture was stirred for 18 hours at room temperature. The reaction liquid was concentrated under reduced pressure and the resultant residue was subjected to preparative thin layer chromatography for purification and then recrystallized from ether-hexane whereby 165 mg (yield: 89.2%) of the title compound was obtained as colorless platelet crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 154.5 - 156.5°C

TLC (silica gel): Rf 0.43 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3360, 1740, 1730, 1650

NMR^δCDCl₃: 0.95 (3H, m, CH₂CH₂CH₃), 1.05 (3H, s, C₁₈-CH₃),

1.23 (6H, d, J=6Hz, -CH₂- $\begin{matrix} \text{CH}_3 \\ | \\ \text{CH} \\ | \\ \text{CH}_3 \end{matrix}$), 1.10-1.18 (3H, m,

C_{6α}-CH₃), 1.46 (3H, s, C₁₉-CH₃), 4.52 (1H, br, C₁₁-CH), 4.75 (2H, d, J=6Hz, C₂₁-CH₂), 6.08 (1H, s, C₄-CH), 6.32 (1H, d, J=10Hz, C₂-CH), 7.32 (1H, d, J=10Hz, C₄-CH)

MS m/e: 515 (M⁺+1), 514 (M⁺), 497, 496, 426, 379, 356, 325,

309, 297, 279, 205, 189, 187, 161, 136, 135, 121,

91, 71 (base peak)

Elementary analysis (as C₃₀H₄₂O₇)

Calc. (%): C 70.01; H 8.23

Found (%): C 70.03; H 8.42

Example 18 11β-Hydroxy-17α-isobutyryloxy-6α-methyl-21-propionyloxy-1,4-pregnadiene-3,20-dione

In 5 ml of benzene was dissolved 120 mg of 11β,21-dihydroxy-17α-isobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 2-(a). To this

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solution were added 130 mg of propionic anhydride and 0.5 ml of pyridine, and the mixture was stirred for 24 hours at room temperature. The reaction mixture was treated in the same manner as described in Example 6 and the resultant crude product was recrystallized from acetone-hexane whereby 120 mg (yield: 88.7%) of the title compound was obtained as colorless needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 128.0 - 131.0°C

TLC (silica gel): R_f 0.41 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3390, 1740, 1720, 1710, 1645

NMRδCDCl₃: 1.08-1.32 (15H, m, -CH<_{CH₃}_{CH₃}, CH₂CH₃, C₁₈-CH₃ and C_{6α}-CH₃), 1.46 (3H, s, C₁₉-CH₃), 4.52 (1H, br, C₁₁-CH), 4.88 (2H, d, J=6Hz, C₂₁-CH₂), 6.00 (1H, s, C₄-CH), 6.23 (1H, d, J=10Hz, C₂-CH), 7.28 (1H, d, J=10Hz, C₁-CH)

MS m/e: 501 (M⁺+1), 500 (M⁺), 482 (M⁺-18), 413, 297, 279, 161, 136 (base peak), 135, 121

Elementary analysis (as C₂₉H₄₀O₇)

Calc. (%):	C 69.57	; H 8.05
Found (%):	C 69.72	; H 8.09

Example 19 11β-Hydroxy-17α,21-diisobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione

In 5 ml of benzene was dissolved 222 mg of 11β,21-dihydroxy-17α-isobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 2-(a). To this solution were added 237 mg of isobutyric anhydride and 0.5 ml of pyridine, and the mixture was stirred for 24 hours

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at room temperature. The reaction liquid was treated in the same manner as described in Example 6 and 171 mg (yield: 66.4%) of the title compound was obtained as colorless needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 165.6 - 166.5°C

TLC (silica gel): Rf 0.43 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3350, 1740, 1720, 1710, 1645

NMRδCDCl₃: 1.05-1.27 (18H, m, -CH₂-CH₃ x 2, C₁₈-CH₃ and

C_{6α}-CH₃), 1.46 (3H, s, C₁₉-CH₃), 4.46 (1H, br, C₁₁-CH), 4.75 (2H, d, J=8Hz, C₂₁-CH₂), 6.02 (1H, s, C₄-CH), 6.27 (1H, d, J=10Hz, C₂-CH), 7.30 (1H, d, J=10Hz, C₁-CH)

MS m/e: 515 (M⁺+1), 514 (M⁺), 496, 427, 297, 279, 161, 136 (base peak), 135, 121

Elementary analysis (as C₃₀H₄₂O₇)

Calc. (%): C 70.01 ; H 8.23

Found (%): C 70.16 ; H 8.21

Example 20 21-Acetoxy-11β-hydroxy-6α-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride were dissolved 147 mg of 11β,21-dihydroxy-6α-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 3. To this solution were added 200 mg of triethylamine and 102 mg of acetic anhydride, and the mixture was stirred for 8 hours at room temperature. To the reaction liquid was added 1 ml of methanol, and the mixture was stirred for further 2 hours.

The reaction liquid was concentrated under reduced pressure and the resultant residue was subjected to preparative thin layer

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chromatography (silica gel) for purification and then recrystallized from ether-hexane whereby 132 mg (yield: 82.5%) of the title compound was obtained as needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 175.0 - 177.0°C

TLC (silica gel): Rf 0.40 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3300, 1755, 1730, 1720, 1650

NMRδCDCl₃: 0.91-1.25 (3H, m, CH₂CH₂CH₂CH₃), 1.02 (3H, s, C₁₈-CH₃), 1.12 (3H, d, J=7Hz, C_{6α}-CH₃), 1.48 (3H, s, C₁₉-CH₃), 2.17 (3H, s, COCH₃), 4.49 (1H, br, C₁₁-CH), 4.78 (2H, d, J=4Hz, C₂₁-CH₂), 6.03 (1H, s, C₄-CH), 6.27 (1H, d, J=10Hz, C₂-CH), 7.29 (1H, d, J=10Hz, C₁-CH)

MS m/e: 501 (M⁺+1), 500 (M⁺), 482, 427, 398, 365, 325, 297, 279, 263, 189, 161, 136 (base peak), 135, 121, 91, 85, 73, 59, 57, 43

Elementary analysis (as C₂₉H₄₀O₇)

Calc. (%): C 69.57 ; H 8.05

Found (%): C 69.43 ; H 8.15

Example 21 21-Butyryloxy-11β-hydroxy-17α-isobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride were dissolved 180 mg of 11β,21-dihydroxy-17α-isobutyryloxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 2-(a). To this solution were added 200 mg of triethylamine and 158 mg of butyric anhydride, and the mixture was stirred for 20 hours at room temperature. To the reaction liquid was added 1 ml of methanol, and the mixture was stirred for

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further 2 hours. The reaction liquid was concentrated under reduced pressure and the resultant residue was subjected to preparative thin layer chromatography for purification and then recrystallized from ether-hexane whereby 168 mg (yield: 81.6%) of the title compound was obtained as colorless platelet crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 121.0 - 123.5°C

TLC (silica gel): Rf 0.43 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3400, 1745, 1730, 1650

NMRδCDCl₃ : 1.00 (3H, m, CH₂CH₂CH₃), 1.06 (3H, s, C₁₈-CH₃),
1.14 (3H, m, C_{6α}-CH₃), 1.16 (6H, d, J=7Hz, -CH<^{CH₃}_{CH₃}),
1.48 (3H, s, C₁₉-CH₃), 4.51 (1H, br, C₁₁-CH), 4.75
(2H, d, J=6.5Hz, C₂₁-CH₂), 6.03 (1H, s, C₄-CH),
6.29 (1H, d, J=10Hz, C₂-CH), 7.29 (1H, d, J=10Hz,
C₁-CH)

MS m/e : 515 (M⁺+1), 514 (M⁺), 497, 496, 426, 413, 379, 356,
325, 297, 279, 221, 205, 189, 161, 136, 135, 121,
91, 71, 43 (base peak)

Elementary analysis (as C₃₀H₄₂O₇)

Calc. (%): C 70.01 ; H 8.23

Found (%): C 69.95 ; H 8.14

Example 22 11β-Hydroxy-17α-isovaleryloxy-6α-methyl-21-propionyloxy-1,4-pregnadiene-3,20-dione

In 5 ml of benzene was dissolved 310 mg of 11β,21-dihydroxy-17α-isovaleryloxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 4. To this solution were added 240 mg of propionic anhydride and 0.5 ml

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of pyridine, and the mixture was stirred for 20 hours at room temperature. The reaction liquid was treated in the same manner as described in Example 6 whereby 279 mg (yield: 80.1%) of the title compound was obtained as colorless needle crystals.

5 Shown below are physical properties and various analytical data of this compound.

M.P. 163.5 - 164.5°C

TLC (silica gel): R_f 0.43 (single spot; benzene:ethanol = 10:1)

10 IR_{max}^{KBr} cm⁻¹ : 3360, 1740, 1720, 1710, 1645

NMRδCDCl₃ : 0.90-1.20 (15H, m, -CH₂CH₂^{CH₃}_{CH₃}, -CH₂CH₃,

C₁₈-CH₃ and C_{6α}-CH₃), 1.42 (3H, s, C₁₉-CH₃),

4.47 (1H, br, C₁₁-CH), 4.77 (2H, d, J=4Hz, C₂₁-CH₂),

15 6.03 (1H, s, C₄-CH), 6.26 (1H, d, J=10Hz, C₂-CH),

7.33 (1H, d, J=10Hz, C₁-CH)

MS m/e : 515 (M⁺+1), 514 (M⁺), 499, 356, 325, 297, 279, 161,
136 (base peak), 135, 121

Elementary analysis (as C₃₀H₄₂O₇)

20 Calc. (%): C 70.01 ; H 8.23

Found (%): C 70.23 ; H 8.45

Example 23 11β-Hydroxy-6α-methyl-21-propionyloxy-17α-
valeryloxy-1,4-pregnadiene-3,20-dione

25 In 3 ml of methylene chloride was dissolved 176 mg of 11β,21-dihydroxy-6α-methyl-17α-valeryloxy-1,4-pregnadiene-3,20-dione. To this solution were added 316 mg of pyridine and 250 mg of propionic anhydride, and the mixture was stirred for 24 hours at room temperature. Next, 50 ml of ethyl acetate was
30 added to the reaction liquid and the liquid mixture was washed successively with 30 ml of water, 1 ml of a 10% solution of

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sodium carbonate, 30 ml of water, 2 ml of 10% HCl and 30 ml of water and then dried over anhydrous sodium sulfate. After filtration of the liquid mixture, the filtrate was concentrated and the resultant residue was subjected to preparative thin layer chromatography (silica gel) for purification whereby 165 mg (yield: 83.3%) of the title compound was obtained as colorless needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 183.0 - 184.0°C

TLC (silica gel): Rf 0.42 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3360, 1740, 1720, 1645

NMRδCDCl₃: 1.00 (6H, t, J=8Hz, CH₂CH₃ x 2), 1.00 (3H, s, C₁₈-CH₃), 1.16 (3H, d, J=6Hz, C_{6α}-CH₃), 1.42 (3H, s, C₁₉-CH₃), 4.47 (1H, br, C₁₁-CH), 4.78 (2H, d, J=5Hz, C₂₁-CH₂), 6.00 (1H, s, C₄-CH), 6.23 (1H, d, J=10Hz, C₂-CH), 7.30 (1H, d, J=10Hz, C₁-CH)

MS m/e: 515 (M⁺+1), 514 (M⁺), 496 (M⁺-18), 297, 279, 161, 136 (base peak), 135, 121,

Elementary analysis (as C₃₀H₄₂O₇)

Calc. (%): C 70.01 ; H 8.23

Found (%): C 69.88 ; H 8.41

Example 24 21-Acetoxy-11β-hydroxy-17α-isovaleryloxy-6α-methyl-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 92 mg of 11β,21-dihydroxy-17α-isovaleryloxy-6α-methyl-1,4-pregnadiene-3,20-dione. To this solution were added 200 mg of triethylamine and 102 mg of acetic anhydride, and the mixture was stirred for 8 hours at room temperature. To the reaction liquid was added 1 ml of methanol, and the mixture was stirred for further 2 hours.

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The reaction liquid was concentrated under reduced pressure and the resultant residue was subjected to preparative thin layer chromatography (silica gel) for purification and then recrystallized from ether-hexane whereby 87 mg (yield: 37.0%) of the title compound was obtained as colorless needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 178.5 - 180.5°C

TLC (silica gel): R_f 0.39 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3340, 1750, 1730, 1720, 1650

NMRδCDCl₃ : 0.91 (3H, m, C₁₈-CH₃), 1.01 (6H, d, J=3Hz,

-CH₂-
CH₃), 1.12 (3H, d, J=7Hz, C_{6α}-CH₃), 1.45

(3H, s, C₁₉-CH₃), 2.15 (3H, s, COCH₃), 4.46 (1H, m, C₁₁-CH), 4.76 (2H, d, J=3.5Hz, C₂₁-CH₂), 6.02 (1H, s, C₄-CH), 6.26 (1H, d, J=10Hz, C₂-CH), 7.27 (1H, d, J=10Hz, C₁-CH)

MS m/e : 501 (M⁺+1), 500 (M⁺), 483, 427, 398, 365, 325, 315, 297, 279, 263, 189, 187, 161, 136 (base peak), 135, 121, 91, 85, 57, 43

Elementary analysis (as C₂₈H₃₈O₇)

Calc. (%): C 69.12 ; H 7.87

Found (%): C 69.33 ; H 8.14

Example 25 17α-Acetoxy-11β-hydroxy-6α-methyl-21-valeryloxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 208 mg of 17α-acetoxy-11β,21-dihydroxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 6. To this solution was added 0.5 ml of pyridine, and the mixture

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was ice-cooled. To the mixture was added slowly a solution of 241 mg of valeryl chloride in 2 ml of methylene chloride, and the mixture was stirred for one hour. To this reaction liquid was added 60 ml of ethyl acetate, and the mixture was washed successively with 30 ml of water, 10 ml of a dilute aqueous solution of sodium carbonate, 30 ml of water, 5 ml of dilute hydrochloric acid and twice 30 ml of water and dried over anhydrous sodium sulfate. After filtration, the filtrate was concentrated and the resultant residue was subjected to preparative thin layer chromatography (silica gel) for purification whereby 186 mg (yield: 87.4%) of the title compound was obtained as colorless needle crystals (recrystallized from ether-hexane). Shown below are physical properties and various analytical data of this compound.

M.P. 148.0 - 150.0°C

TLC (silica gel): Rf 0.42 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹: 3360, 1750, 1730, 1650

¹H NMR δCDCl₃: 0.93 (3H, m, CH₂CH₂CH₂CH₃), 1.03 (3H, s, C₁₈-CH₃), 1.12 (3H, d, J=7Hz, C_{6α}-CH₃), 1.46 (3H, s, C₁₉-CH₃), 2.05 (3H, s, COCH₃), 4.49 (1H, br, C₁₁-CH), 4.76 (2H, d, J=4Hz, C₂₁-CH₂), 6.03 (1H, s, C₄-CH), 6.27 (1H, d, J=10Hz, C₂-CH), 7.29 (1H, d, J=10Hz, C₁-CH)

MS m/e: 501 (M⁺+1), 500 (M⁺), 483 (M⁺-17), 482 (M⁺-18), 440, 425, 356, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 85, 57, 43

Elementary analysis (as C₂₉H₄₀O₇)

Calc. (%): C 69.57 ; H 8.05

Found (%): C 69.60 ; H 8.15

Example 26 17α-Acetoxy-11β-hydroxy-21-isovaleryloxy-6α-

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methyl-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 208 mg of 11 β ,21-dihydroxy-17 α -acetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 6. To this solution was added 202 mg of triethylamine and the solution was cooled externally with ice. To this solution was added slowly a solution of 120 mg of isovaleryl chloride in 1 ml of methylene chloride, and the mixture was stirred for 1.5 hours. To the reaction liquid was added 1 ml of methanol, and the mixture was further stirred for one hour. The reaction liquid was concentrated under reduced pressure and the resultant residue was directly subjected to preparative thin layer chromatography (silica gel) for purification and then recrystallized from ether-hexane whereby 195 mg (yield: 78.0%) of the title compound was obtained as colorless fine needle crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 126.5 - 129.5°C

TLC (silica gel): R_f 0.41 (single spot; benzene:ethanol = 10;1)IR_{max}^{KBr} cm⁻¹ : 3400, 1740, 1730, 1650

NMR δ CDCl₃ : 0.92 (3H, s, C₁₈-CH₃), 1.03 (6H, s-like, -CH₂-CH₃), 1.08 (3H, d, J=6Hz, C_{6 α} -CH₃), 1.45 (3H, s, C₁₉-CH₃), 2.02 (3H, s, COCH₃), 4.49 (1H, br, C₁₁-CH), 4.76 (2H, d, J=4Hz, C₂₁-CH₂), 6.02 (1H, s, C₄-CH), 6.26 (1H, d, J=10Hz, C₂-CH), 7.29 (1H, d, J=10Hz, C₁-CH)

MS m/e : 501 (M⁺+1), 500 (M⁺), 483, 482, 440, 425, 356, 325, 297, 279, 189, 161, 136 (base peak), 135, 121, 85,

57, 43

Elementary analysis (as C₂₉H₄₀O₇)

Calc. (%): C 69.57 ; H 8.05

Found (%): C 69.46 ; H 8.10

Example 27 11 β -Hydroxy-6 α -methyl-17 α -propionyloxy-21-valeryloxy-
1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 215 mg of 11 β ,21-dihydroxy-6 α -methyl-17 α -propionyloxy-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 7. To this solution was added 348 mg of diethylmethylamine, and the mixture was cooled externally with ice. To the solution was slowly added 240 mg of valeryl chloride, and the mixture was stirred for 1.5 hours. To the reaction liquid was added 2 ml of methanol, and the mixture was further stirred for 2 hours. The reaction liquid was concentrated under reduced pressure and the resultant residue was subjected directly to preparative thin layer chromatography (silica gel) for purification and then recrystallized from ether-hexane whereby 204 mg (yield: 79.4%) of the title compound was obtained as colorless platelet crystals. Shown below are physical properties and various analytical data of this compound.

M.P. 141.5 - 143.0°C

TLC (silica gel): R_f 0.43 (single spot; benzene:ethanol = 10:1)

IR_{max}^{KBr} cm⁻¹ : 3400, 1745, 1730, 1655

NMR δ CDCl₃ : 0.94-1.25 (6H, m, CH₂CH₃ and CH₂CH₂CH₂CH₃), 1.07 (3H, s, C₁₈-CH₃), 1.14 (3H, d, J=6Hz, C_{6 α} -CH₃), 1.48 (3H, s, C₁₉-CH₃), 4.49 (1H, br, C₁₁-CH), 4.79 (2H, d, J=4Hz, C₂₁-CH₂), 6.03 (1H, s, C₄-CH), 6.28 (1H, d, J=10Hz, C₂-CH), 7.32 (1H, d, J=10Hz, C₁-CH)
MS m/e : 515 (M⁺+1), 514 (M⁺), 497, 496, 440, 425, 399, 379, 356, 338, 297, 279, 189, 187, 161, 136 (base peak), 135, 91, 85, 57

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Elementary analysis (as $C_{30}H_{42}O_7$)

Calc. (%): C 70.01 ; H 8.23

Found (%): C 69.79 ; H 8.07

Example 28 11 β -Hydroxy-21-isovaleryloxy-6 α -methyl-17 α -
propionyloxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 215 mg of
11 β ,21-dihydroxy-6 α -methyl-17 α -propionyloxy-1,4-pregnadiene-
3,20-dione obtained according to the method as described in
Example 7. To this solution was added 202 mg of triethylamine,
and the mixture was stirred under external ice-cooling. To
this solution was added slowly 120 mg of isovaleryl chloride, and
the mixture was stirred for one hour. After the addition of 1 ml
of methanol, the mixture was further stirred for one hour. The
reaction liquid was concentrated under reduced pressure and the
resultant residue was subjected directly to preparative thin
layer chromatography (silica gel) for purification and then
recrystallized from ether-hexane whereby 211 mg (yield: 82.1%)
of the title compound was obtained as colorless platelet crystals.
Shown below are physical properties and various analytical data
of this compound.

M.P. 124.5 - 126.0°C

TLC (silica gel): R_f 0.42 (single spot; benzene:ethanol = 10:1)IR_{max}^{KBr} cm⁻¹: 3380, 1740, 1730, 1650

NMR δ CDCl₃: 0.93 (3H, s, C₁₈-CH₃), 0.95-1.21 (6H, m, C_{6 α} -CH₃
and CH₂CH₃), 1.02 (6H, s, -CH₂-CH₂-CH₃), 1.48 (3H, s,
C₁₉-CH₃), 4.48 (1H, br, C₁₁-CH), 4.76 (2H, d, J=6Hz,
C₂₁-CH₂), 6.01 (1H, s, C₄-CH), 6.25 (1H, d, J=10Hz,
C₂-CH), 7.30 (1H, d, J=10Hz, C₁-CH)

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MS m/e : 515 ($M^+ + 1$), 514 (M^+), 497, 496, 440, 425, 399, 379,
356, 338, 325, 297, 279, 189, 187, 161, 136 (base peak),
135, 121, 91, 85, 57

Elementary analysis (as $C_{30}H_{42}O_7$)

Calc. (%): C 70.01 ; H 8.23

Found (%): C 69.86 ; H 8.35

Example 29 11 β -Hydroxy-21-methoxyacetoxy-6 α -methyl-17 α -
propionyloxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 215 mg of 11 β ,21-
dihydroxy-6 α -methyl-17 α -propionyloxy-1,4-pregnadiene-3,20-dione.
To this solution were added 180 mg of methoxyacetic acid and 412
mg of N,N'-dicyclohexylcarbodiimide, and the mixture was stirred
for 48 hours at room temperature. The solvent was distilled off
and 50 ml of ethyl acetate was added to the residue. The mixture
was washed with 2 ml of a dilute aqueous solution of Na_2CO_3 and
20 ml of water. The ethyl acetate layer was washed twice with 20 ml
of water, dried over anhydrous sodium sulfate and then filtered.
The filtrate was concentrated and the resultant residue was
subjected to preparative thin layer chromatography whereby 184 mg
(yield: 73.3%) of the title compound was obtained. This compound
was a colorless amorphous solid but its structure was confirmed as
a result of the following analyses:

IR $_{\max}^{KBr}$ cm^{-1} : 3440 (OH), 1760, 1730, 1720, 1655

NMR δ CDCl $_3$: 1.06 (3H, s, C $_{18}$ -CH $_3$), 1.20 (3H, t, J=7.0Hz,
-CH $_2$ CH $_3$), 1.22 (3H, d, J=6Hz, C $_{6\alpha}$ -CH $_3$), 1.46 (3H,
s, C $_{19}$ -CH $_3$), 3.48 (3H, s, OCH $_3$), 4.20 (2H, s, COCH $_2$ O)

MS m/e : 503 ($M^+ + 1$), 502 (M^+), 484, 428, 297, 279, 136 (base
peak), 135, 91, 74, 73, 57, 45

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Elementary analysis (as $C_{28}H_{38}O_8$)

Calc. (%): C 66.91 ; H 7.62

Found (%): C 67.17 ; H 7.53

5 Example 30 17 α -Butyryloxy-11 β -hydroxy-21-methoxyacetoxy-
6 α -methyl-1,4-pregnadiene-3,20-dione

Using 222 mg of 17 α -butyryloxy-11 β ,21-dihydroxy-6 α -methyl-
1,4-pregnadiene-3,20-dione obtained according to the method as
described in Example 1-(a), the reaction with methoxyacetic acid
was carried out in the same manner as described in Example 29
10 and the after-treatment was also carried out similarly to obtain
the title compound. This crude product was then recrystallized
from ether-hexane to give 179 mg (yield: 69.4%) of the pure
product as colorless needle crystals.

M.P. 111.5 - 113.0°C

15 IR_{max}^{KBr} cm^{-1} : 3400 (OH), 1760, 1745, 1725, 1650

NMR δ CDCl₃ : 0.92-1.08 (3H, m, CH₂CH₂CH₃), 1.04 (3H, s, C₁₈-CH₃),
1.10 (3H, d, J=6Hz, C_{6 α} -CH₃), 1.44 (3H, s, C₁₉-CH₃),
3.48 (3H, s, OCH₃), 4.18 (2H, s, COCH₂O)

20 MS m/e : 517 (M⁺+1), 516 (M⁺), 499, 498, 325, 297, 279, 161,
136 (base peak), 135, 121, 91, 71, 45

Elementary analysis (as $C_{29}H_{40}O_8$)

Calc. (%): C 67.42 ; H 7.80

Found (%): C 67.37 ; H 7.85

25 Example 31 11 β -Hydroxy-17 α -isobutyryloxy-21-methoxyacetoxy-
6 α -methyl-1,4-pregnadiene-3,20-dione

Using 215 mg of 11 β ,21-dihydroxy-17 α -isobutyryloxy-6 α -
methyl-1,4-pregnadiene-3,20-dione obtained according to the
method as described in Example 2-(a), the reaction with

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methoxyacetic acid was carried out in the same manner as described in Example 29 and the after-treatment was also carried out similarly to obtain the title compound. This crude product was recrystallized from ether-hexane to give 192 mg (yield: 77.4%) of the pure product.

M.P. 119.0 - 121.0°C

IR_{max}^{KBr} cm⁻¹ : 3420 (OH), 1760, 1730, 1715, 1655

NMRδCDCl₃ : 1.07 (3H, s, C₁₈-CH₃), 1.12 (6H, d, J=8Hz, CH(CH₃)₂), 1.48 (3H, s, C₁₉-CH₃), 3.47 (3H, s, OCH₃), 4.17 (2H, COCH₂O)

MS m/e : 517 (M⁺+1), 516 (M⁺), 498, 427, 325, 297, 279, 161, 136 (base peak), 135, 73, 71, 45

Elementary analysis (as C₂₉H₄₀O₈)

Calc. (%): C 67.42 ; H 7.80

Found (%): C 67.28 ; H 7.93

Example 32 11β,21-Dihydroxy-17α-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione

In 4 ml of dimethylformamide was dissolved 748 mg of 6α-methylprednisolone. To this solution was added 768 mg of ethyl orthomethoxyacetate, and the mixture was heated at 75°C under an argon current. To the reaction liquid was then added 17 mg of anhydrous p-toluenesulfonic acid, and the mixture was stirred for 2 hours at the same temperature. The reaction mixture was then treated in the same manner as described in Example 1-(a) whereby 826 mg (yield: 87.1%) of 6α-methylprednisolone 17α,21-ethyl orthomethoxyacetate was obtained as colorless needle crystals. This compound was a mixture of its stereoisomers.

The ethyl orthomethoxyacetate used in this Example was obtained by reacting methoxyacetonitrile with hydrogen chloride

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in dry ethanol and then treating the resultant ethyl iminoether hydrochloride with ethanol. B.P. 177.0 - 180.0°C.

In 8 ml of methanol was dissolved 237 mg of the above 6 α -methylprednisolone 17 α ,21-ethyl orthomethoxyacetate. To this solution was 1 ml of 2N-oxalic acid, and the mixture was warmed at 40°C for 10 minutes. The solvent was removed by distillation under reduced pressure and the residue was treated in the same manner as described in Example 1-(b) whereby 138 mg (yield: 61.9%) of the title compound was obtained as a colorless amorphous solid. The structure of this compound was confirmed by the following analytical results:

IR_{max}^{KBr} cm⁻¹ : 3420 (OH), 1740, 1720, 1655

NMR δ CDCl₃ : 1.10 (3H, s, C₁₈-CH₃), 1.26 (3H, d, J=6Hz, C_{6 α} -CH₃), 1.47 (3H, s, C₁₉-CH₃), 3.39 (3H, s, OCH₃), 4.00 (2H, s, COCH₂O), 4.35 (2H, s, C₂₁-CH₂), 4.51 (1H, br.s, C₁₁-CH), 6.08 (1H, s, C₄-CH), 6.33 (1H, d, J=10Hz, C₂-CH), 7.26 (1H, d, J=10Hz, C₁-CH)

MS m/e : 447 (M⁺+1), 446 (M⁺), 428, 357, 298, 161, 136 (base peak), 135, 121, 45

Elementary analysis (as C₂₅H₃₄O₇)

Calc. (%): C 67.25 ; H 7.67

Found (%): C 67.01 ; H 7.81

Example 33 21-Acetoxy-11 β -hydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 223 mg of 11 β ,21-dihydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 32. To this solution were added 404 mg of triethylamine and 204 mg of acetic anhydride, and the mixture was stirred for 5 hours at

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room temperature. The reaction mixture was then treated in the same manner as described in Example 7 whereby 186 mg (yield: 76.2%) of the title compound was obtained as colorless needle crystals.

M.P. 149.5 - 151.5°C

$\text{IR}_{\text{max}}^{\text{KBr cm}^{-1}}$: 3320 (OH), 1760, 1730, 1720, 1655

$\text{NMR}_{\text{CDCl}_3}$: 1.05 (3H, s, C_{18} - CH_3), 1.13 (3H, d, $J=6\text{Hz}$, $\text{C}_{6\alpha}$ - CH_3), 1.48 (3H, s, C_{19} - CH_3), 2.14 (3H, s, COCH_3), 3.42 (3H, s, OCH_3), 3.99 (2H, s, COCH_2O)

MS m/e : 489 (M^++1), 488 (M^+), 470, 398, 325, 297, 279, 161, 136 (base peak), 135, 121, 45, 43

Elementary analysis (as $\text{C}_{27}\text{H}_{36}\text{O}_8$)

Calc. (%): C 66.38 ; H 7.43

Found (%): C 66.30 ; H 7.56

Example 34 11 β -Hydroxy-17 α -methoxyacetoxy-6 α -methyl-21-propionyloxy-1,4-pregnadiene-3,20-dione

In 2 ml of methylene chloride was dissolved 223 mg of 11 β ,21-dihydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 32. To this solution were added 404 mg of triethylamine and 208 mg of propionic anhydride, and the mixture was stirred for 5 hours at room temperature. The reaction mixture was then treated in the same manner as described in Example 7 whereby 157 mg (yield: 62.5%) of the title compound was obtained as colorless needle crystals.

M.P. 114.5 - 116.5°C

$\text{IR}_{\text{max}}^{\text{KBr cm}^{-1}}$: 3420 (OH), 1750, 1740-1730, 1655

$\text{NMR}_{\text{CDCl}_3}$: 1.06 (3H, s, C_{18} - CH_3), 1.17 (3H, m, CH_2CH_3),

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1.22 (3H, d, J=6Hz, C_{6α}-CH₃), 1.47 (3H, s, C₁₉-CH₃),3.40 (3H, s, OCH₃), 4.00 (2H, s, COCH₂O)MS m/e : 503 (M⁺+1), 502 (M⁺), 484, 412, 398, 325, 297, 279,

161, 136 (base peak), 135, 121, 57, 45

5 Elementary analysis (as C₂₈H₃₈O₈)

Calc. (%): C 66.91 ; H 7.62

Found (%): C 67.13 ; H 7.58

Example 35 21-Butyryloxy-11β-hydroxy-17α-methoxyacetoxy-6α-
methyl-1,4-pregnadiene-3,20-dione

10

In 2 ml of methylene chloride was dissolved 223 mg of
11β,21-dihydroxy-17α-methoxyacetoxy-6α-methyl-1,4-pregnadiene-
3,20-dione obtained according to the method as described in
Example 32. To this solution were added 404 mg of triethylamine
and 253 mg of butyric anhydride, and the mixture was stirred for
5 hours at room temperature. The reaction mixture was then
treated in the same manner as described in Example 7 whereby
178 mg (yield: 69.0%) of the title compound was obtained as
colorless needle crystals.

15

20

M.P. 132.0 - 133.5°C

IR_{max}^{KBr} cm⁻¹ : 3440 (OH), 1745, 1740-1730, 1655NMRδCDCl₃ : 1.10 (3H, s, C₁₈-CH₃), 1.15 (3H, m, CH₂CH₃),

25

1.47 (3H, s, C₁₉-CH₃), 3.42 (3H, s, OCH₃), 4.00(2H, s, COCH₂O)MS m/e : 517 (M⁺+1), 516 (M⁺), 498 (M⁺-18), 426, 412, 356,

297, 279, 136 (base peak), 135, 121, 71, 45

Elementary analysis (as C₂₉H₄₀O₈)

30

Calc. (%): C 67.42 ; H 7.80

Found (%): C 67.48 ; H 7.71

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Example 36 11 β -Hydroxy-21-isobutyryloxy-17 α -methoxyacetoxy-
6 α -methyl-1,4-pregnadiene-3,20-dione

In 2 ml of methylene chloride was dissolved 223 mg of
11 β ,21-dihydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-
3,20-dione obtained according to the method as described in
Example 32. To this solution were added 404 mg of triethylamine
and 253 mg of isobutyric anhydride, and the mixture was stirred
for 5 hours at room temperature. The reaction mixture was then
treated in the same manner as described in Example 7 whereby
168 mg (yield: 65.1%) of the title compound was obtained as
colorless needle crystals.

M.P. 148.0 - 149.5°C

IR_{max}^{KBr} cm⁻¹ : 3400 (OH), 1750, 1740-1730, 1655

NMR δ CDCl₃ : 1.10 (3H, s, C₁₈-CH₃), 1.23 (6H, d, J=7Hz,
CH(CH₃)₂), 1.48 (3H, s, C₁₉-CH₃), 3.42 (3H, s, OCH₃),
4.01 (2H, s, COCH₂O)

MS m/e : 517 (M⁺+1), 516 (M⁺), 498, 426, 325, 297, 279,
136 (base peak), 135, 121, 71, 45

Elementary analysis (as C₂₉H₄₀O₈)

Calc. (%): C 67.42 ; H 7.80

Found (%): C 67.28 ; H 7.97

Example 37 11 β -Hydroxy-17 α ,21-di(methoxyacetoxy)-6 α -methyl-
1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 223 mg of
11 β ,21-dihydroxy-17 α -methoxyacetoxy-6 α -methyl-1,4-pregnadiene-
3,20-dione obtained according to the method as described in
Example 32. To this solution were added 216 mg of methoxyacetic
acid and 453 mg of N,N'-dicyclohexylcarbodiimide, and the
mixture was stirred for 46 hours at room temperature. The

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reaction mixture was then treated in the same manner as described in Example 29 whereby 157 mg (yield: 60.6%) of the title compound was obtained. This compound was a colorless amorphous solid but its structure was confirmed by the following analytical results:

5 IR_{max}^{KBr} cm⁻¹ : 3440 (OH), 1760, 1745, 1730, 1655

NMRδCDCl₃ : 1.06 (3H, s, C₁₈-CH₃), 1.12 (3H, d, J=6Hz, C_{6α}-CH₃), 1.43 (3H, s, C₁₉-CH₃), 3.42 (3H, s, C₁₇-OOCH₂OCH₃), 3.49 (3H, s, C₂₁-OOCH₂OCH₃), 4.00 (2H, s, C₁₇-OOCH₂), 4.20 (2H, s, C₂₁-OOCH₂)

10 MS m/e : 519 (M⁺+1), 518 (M⁺), 500, 428, 325, 297, 279, 161
136 (base peak), 135, 121, 60, 45

Elementary analysis (as C₂₈H₃₈O₉)

Calc. (%): C 64.85 ; H 7.39

15 Found (%): C 64.91 ; H 7.27

Example 38 11β-Hydroxy-6α-methyl-21-methylthioacetoxyl-17α-propionyloxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 235 mg of 11β,21-dihydroxy-6α-methyl-17α-propionyloxy-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 7. To this solution were added 202 mg of triethylamine and 266 mg of methylthioacetic anhydride, and the mixture was stirred for one hour at room temperature. The reaction mixture was then treated in the same manner as described in Example 7 whereby 207 mg (yield: 72.6%) of the title compound was obtained as colorless needle crystals.

M.P. 126.0 - 127.5°C

30 IR_{max}^{KBr} cm⁻¹ : 3400 (OH), 1745, 1730, 1715, 1650

NMRδCDCl₃ : 1.06 (3H, s, C₁₈-CH₃), 1.12 (3H, t, J=8Hz, CH₂CH₃), 1.46 (3H, s, C₁₉-CH₃), 2.25 (3H, s, SCH₃), 3.31 (2H,

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s, COCH₂S)

MS m/e : 519 (M⁺+1), 518 (M⁺), 426, 356, 325, 297, 279, 161, 136
135, 121, 61 (base peak), 57

Elementary analysis (as C₂₈H₃₈O₇S)

5 Calc. (%): C 64.84 ; H 7.38

Found (%): C 64.63 ; H 7.31

Example 39 17α-Butyryloxy-11β-hydroxy-6α-methyl-21-
methylthioacetox-1,4-pregnadiene-3,20-dione

10 Using 335 mg of 17α-butyryloxy-11β,21-dihydroxy-6α-methyl-
1,4-pregnadiene-3,20-dione obtained according to the method
as described in Example 1-(a), the reaction with methylthioacetic
anhydride was carried out in the same manner as described in
Example 38, and the reaction mixture was treated in the same
15 manner as described in Example 7 whereby 294 mg (yield: 73.7%)
of the title compound was obtained as colorless needle crystals.

M.P. 173.0 - 174.0°C

IR_{max}^{KBr} cm⁻¹ : 3360, 1740, 1720, 1710, 1650

20 NMRδCDCl₃ : 1.07 (3H, s, C₁₈-CH₃), 1.48 (3H, s, C₁₉-CH₃),
2.25 (3H, s, SCH₃), 3.34 (2H, s, COCH₂S)

MS m/e : 533 (M⁺+1), 532 (M⁺), 443, 429, 425, 397, 325, 297,
279, 161, 136, 135, 121, 71, 61 (base peak)

Elementary analysis (as C₂₉H₄₀O₇S)

25 Calc. (%): C 65.39 ; H 7.57

Found (%): C 65.52 ; H 7.55

Example 40 11β-Hydroxy-17α-isobutyryloxy-6α-methyl-21-
methylthioacetox-1,4-pregnadiene-3,20-dione

30 Using 80 mg of 11β,21-dihydroxy-17α-isobutyryloxy-6α-
methyl-1,4-pregnadiene-3,20-dione obtained according to the

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method as described in Example 2-(a), the reaction with methylthioacetic anhydride was carried out in the same manner as described in Example 38, and the reaction mixture was treated in the same manner as described in Example 7 whereby 86 mg (yield: 89.6%) of the title compound was obtained as colorless needle crystals.

M.P. 136.0 - 138.0°C

IR_{max}^{KBr} cm⁻¹ : 3320, 1750, 1730, 1710, 1650

NMRδCDCl₃ : 1.05 (3H, s, C₁₈-CH₃), 1.12 (6H, d, J=8Hz, CH(CH₃)₂), 1.46 (3H, s, C₁₉-CH₃), 2.25 (3H, s, SCH₃), 3.31 (2H, s, COCH₂S)

MS m/e : 533 (M⁺+1), 532 (M⁺), 429, 325, 297, 279, 161, 136, 135, 121, 71, 61 (base peak)

Elementary analysis (as C₂₉H₄₀O₇S)

Calc. (%): C 65.39 ; H 7.57

Found (%): C 65.26 ; H 7.65

Example 41 11β-Hydroxy-17α-methoxyacetoxy-6α-methyl-21-methylthioacetoxy-1,4-pregnadiene-3,20-dione

Using 150 mg of 11β,21-dihydroxy-17α-methoxyacetoxy-6α-methyl-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 32, the reaction with methylthioacetic anhydride was carried out in the same manner as described in Example 38 and the reaction mixture was treated in the same manner as described in Example 7 whereby 123 mg (yield: 68.3%) of the title compound was obtained as a colorless amorphous solid. The structure of this compound was confirmed by the following analytical results:

IR_{max}^{KBr} cm⁻¹ : 3420, 1745, 1730, 1720, 1655

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NMR δ CDCl₃ : 1.10 (3H, s, C₁₈-CH₃), 1.22 (3H, d, J=6Hz, C_{6 α} -CH₃),
 1.48 (3H, s, C₁₉-CH₃), 2.28 (3H, s, SCH₃), 3.37 (2H,
 s, COCH₂S), 3.46 (3H, s, OCH₃), 4.03 (2H, s, COCH₂O)
 MS m/e : 535 (M⁺+1), 534 (M⁺), 445, 356, 325, 297, 279, 161,
 136, 135, 121, 61, 45 (base peak)

Elementary analysis (as C₂₈H₃₈O₈S)

Calc. (%): C 62.90 ; H 7.16

Found (%): C 63.04 ; H 7.09

Example 42 11 β ,21-Dihydroxy-6 α -methyl-17 α -methylthioacetox-
 1,4-pregnadiene-3,20-dione

In 8 ml of dimethylformamide was dissolved 1.88 g of 6 α -
 methylprednisolone. To this solution was added 1.6 g of ethyl
 orthomethylthioacetate, and the mixture was heated at 75°C under
 an argon current. To this reaction liquid was then added 43 mg
 of anhydrous p-toluenesulfonic acid, and the mixture was stirred
 for one hour at the same temperature. The reaction mixture was
 then treated in the same manner as described in Example 1-(a)
 whereby 2.15 g (yield: 87.8%) of 6 α -methylprednisolone 17 α ,21-
 ethyl orthomethylthioacetate was obtained as colorless needle
 crystals.

M.P. 184.0 - 186.0°C

IR_{max}^{KBr} cm⁻¹ : 3560, 1715, 1660

NMR δ CDCl₃ : 0.87 (3H, s, C₁₈-CH₃), 1.10 (3H, t, J=7Hz, CH₂CH₃),
 1.12 (3H, d, J=6Hz, C_{6 α} -CH₃), 1.47 (3H, s, C₁₉-CH₃),
 2.16 (3H, s, SCH₃), 2.84 (2H, s, COCH₂SCH₃), 3.57 (2H,
 q, J=7Hz, CH₂CH₃)

MS m/e : 491 (M⁺+1), 490 (M⁺), 445, 429, 357, 297, 279, 161
 136, 135 (base peak), 121, 61

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Elementary analysis (as $C_{27}H_{38}O_6S$)

Calc. (%): C 66.09 ; H 7.81

Found (%): C 66.13 ; H 7.75

To 6 ml of methanol was dissolved 210 mg of the above 6 α -methylprednisolone 17 α ,21-ethyl orthomethylthioacetate. To this solution was added 0.5 ml of 2N-oxalic acid, and the mixture was stirred for 10 minutes at 40°C. The solvent was removed by distillation under reduced pressure and the residue was treated in the same manner as described in Example 1-(b) whereby 143 mg (yield: 71.9%) of the title compound was obtained as a colorless amorphous solid. The structure of this compound was confirmed by the following analytical results:

IR_{max}^{KBr} cm^{-1} : 3440, 1720, 1715, 1650

NMR δ CDCl₃ : 0.98 (3H, s, C₁₈-CH₃), 1.12 (3H, d, J=6Hz, C_{6 α} -CH₃), 1.48 (3H, s, C₁₉-CH₃), 2.16 (3H, s, SCH₃), 3.15 (2H, s, COCH₂S)

MS m/e : 463 (M⁺+1), 462 (M⁺), 444, 431, 356, 325, 297, 279, 161, 136, 135, 121, 91, 61 (base peak)

Elementary analysis (as $C_{25}H_{34}O_6S$)

Calc. (%): C 64.91 ; H 7.44

Found (%): C 65.03 ; H 7.38

Example 43 11 β -Hydroxy-21-methoxyacetoxy-6 α -methyl-17 α -methylthioacetoxy-1,4-pregnadiene-3,20-dione

In 4 ml of methylene chloride was dissolved 180 mg of 11 β ,21-dihydroxy-6 α -methyl-17 α -methylthioacetoxy-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 42. To this solution were added methoxyacetic anhydride prepared separately from methoxyacetic acid and then triethylamine,

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and the mixture was stirred for one hour at room temperature.
The reaction mixture was then treated in the same manner as described in Example 7 whereby 259 mg (yield: 89.6%) of the title compound was obtained as colorless needle crystals.

5 M.P. 112.0 - 114.0°C

IR_{max}^{KBr} cm⁻¹ : 3360, 1760, 1740, 1720, 1650

NMRδCDCl₃ : 1.07 (3H, s, C₁₈-CH₃), 1.23 (3H, d, J=6.5Hz, C_{6α}-CH₃), 1.49 (3H, s, C₁₉-CH₃), 2.18 (3H, s, SCH₃), 3.13 (2H, s, COCH₂S), 3.47 (3H, s, COCH₂OCH₃), 4.20 (2H, s, COCH₂OCH₃)

MS m/e : 535 (M⁺+1), 534 (M⁺), 517, 516, 427, 413, 325, 297, 293, 279, 161, 136, 135, 121, 91, 61 (base peak), 45

Elementary analysis (as C₂₈H₃₈O₈S)

Calc. (%): C 62.90 ; H 7.16

15 Found (%): C 62.82 ; H 7.25

Example 44 11β-Hydroxy-6α-methyl-17α,21-di(methylthioacetox)-1,4-pregnadiene-3,20-dione

Using 250 mg of 11β,21-dihydroxy-6α-methyl-17α-methylthioacetox-1,4-pregnadiene-3,20-dione obtained according to the method as described in Example 42, the reaction with methylthioacetic anhydride was carried out in the same manner as described in Example 38 and the reaction mixture was treated in the same manner as described in Example 7 whereby 215 mg (yield: 72.4%) of the title compound was obtained as colorless needle crystals.

25 M.P. 175.0 - 177.0°C

IR_{max}^{KBr} cm⁻¹ : 3370, 1740, 1725, 1720, 1655

NMRδCDCl₃ : 1.06 (3H, s, C₁₈-CH₃), 1.15 (3H, d, J=4Hz, C_{6α}-CH₃), 1.47 (3H, s, C₁₉-CH₃), 2.19 (3H, s, C₁₇-OCOCH₂SCH₃),

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2.25 (3H, s, C₂₁-OCOCH₂SCH₃), 3.12 (2H, s, C₁₇-OCOCH₂S),3.33 (2H, s, C₂₁-OCOCH₂S)MS m/e : 551 (M⁺+1), 550 (M⁺), 444, 426, 356, 325, 297, 279,

161, 136, 135, 121, 61 (base peak)

5 Elementary analysis (as C₂₈H₃₈O₇S₂)

Calc. (%): C 61.07 ; H 6.95

Found (%): C 61.22 ; H 6.82

Example 45 21-Acetoxy-11 β -hydroxy-6 α -methylthioacetoxy-
1,4-pregnadiene-3,20-dione

10 Using 232 mg of 11 β ,21-dihydroxy-6 α -methyl-17 α -methylthio-
acetoxy-1,4-pregnadiene-3,20-dione obtained according to the
method as described in Example 42, the reaction with acetic
anhydride was carried out in the same manner as described in
Example 7 and the reaction mixture was treated similarly whereby 213mg
15 (yield: 84.5%) of the title compound was obtained as colorless
needle crystals.

M.P. 149.0 - 151.0°C

IR_{max}^{KBr} cm⁻¹ : 3400, 1760, 1725, 1720, 1650,NMR δ CDCl₃ : 1.03 (3H, s, C₁₈-CH₃), 1.10 (3H, d, J=8Hz, C_{6 α} -CH₃),

20 1.47 (3H, s, C₁₉-CH₃), 2.15 (3H, s, SCH₃), 2.19 (3H,
s, COCH₃), 3.12 (2H, s, COCH₂S)

MS m/e : 505 (M⁺+1), 504 (M⁺), 356, 325, 297, 279, 161, 136

135, 121, 61 (base peak), 43

Elementary analysis (as C₂₇H₃₆O₇S)

25 Calc. (%): C 64.26 ; H 7.19

Found (%): C 64.47 ; H 7.14

Example 46 11 β -Hydroxy-6 α -methyl-17 α -methylthioacetoxy-
21-propionyloxy-1,4-pregnadiene-3,20-dione

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Using 232 mg of 11 β ,21-dihydroxy-6 α -methyl-17 α -methylthio-
acetoxo-1,4-pregnadiene-3,20-dione obtained according to the
method as described in Example 42, the reaction with propionic
anhydride was carried out in the same manner as described in
Example 18 with exception that triethylamine was used instead
of pyridine, and the reaction mixture was treated in the same
manner as described in Example 7 whereby 224 mg (yield: 86.5%)
of the title compound was obtained as colorless needle crystals.
M.P. 117.0 - 119.0°C

IR $_{\text{max}}^{\text{KBr}}$ cm $^{-1}$: 3400, 1745, 1725, 1715, 1650

NMR δ CDCl $_3$: 1.02 (3H, s, C $_{18}$ -CH $_3$), 1.15 (3H, t, J=8Hz, CH $_2$ CH $_3$),
1.45 (3H, s, C $_{19}$ -CH $_3$), 2.16 (3H, s, SCH $_3$), 3.12 (2H,
s, COCH $_2$ S)

MS m/e : 519 (M $^{+}+1$), 518 (M $^{+}$), 500, 325, 297, 279, 161, 136
135, 121, 91, 61 (base peak), 57

Elementary analysis (as C $_{28}$ H $_{38}$ O $_7$ S)

Calc. (%): C 64.84 ; H 7.38

Found (%): C 64.92 ; H 7.61

Example 47 21-Butyryloxy-11 β -hydroxy-6 α -methyl-17 α -
methylthioacetoxo-1,4-pregnadiene-3,20-dione

Using 232 mg of 11 β ,21-dihydroxy-6 α -methyl-17 α -methylthio-
acetoxo-1,4-pregnadiene-3,20-dione obtained according to the
method as described in Example 42, the reaction with butyric
anhydride was carried out in the same manner as described in
Example 10 and the reaction mixture was treated similarly
whereby 231 mg (yield: 86.8%) of the title compound was obtained.
M.P. 126.0 - 128.0°C

IR $_{\text{max}}^{\text{KBr}}$ cm $^{-1}$: 3380, 1745, 1725, 1715, 1650

NMR δ CDCl₃ : 1.00 (3H, s, C₁₈ -CH₃), 1.02 (3H, t, J=8Hz, CH₂CH₂CH₃), 1.44 (3H, s, C₁₉ -CH₃), 2.18 (3H, s, SCH₃), 3.10 (2H, s, COCH₂S)

MS m/e : 533 (M⁺+1), 532 (M⁺), 514, 325, 297, 279, 161, 136, 135, 121, 91, 71, 61 (base peak)

Elementary analysis (as C₂₉H₄₀O₇S)

Calc. (%): C 65.39 ; H 7.57

Found (%): C 65.51 ; H 7.30

Example 48 11 β -Hydroxy-21-isobutyryloxy-6 α -methyl-

17 α -methylthioacetoxyl-4-pregnadiene-3,20-dione

Using 232 mg of 11 β ,21-dihydroxy-6 α -methyl-17 α -methylthioacetoxyl-4-pregnadiene-3,20-dione, the reaction with isobutyric anhydride was carried out in the same manner as described in

Example 11 and the reaction mixture was treated similarly

whereby 224 mg (yield: 84.2%) of the title compound was obtained as colorless needle crystals.

M.P. 151.0 - 152.0°C

IR ν _{max}^{KBr} cm⁻¹ : 3360, 1745, 1725, 1715, 1650

NMR δ CDCl₃ : 1.02 (3H, s, C₁₈ -CH₃), 1.22 (6H, d, J=7Hz, CH(CH₃)₂), 1.44 (3H, s, C₁₉ -CH₃), 2.18 (3H, s, SCH₃), 3.10 (2H, s, COCH₂S)

MS m/e : 533 (M⁺+1), 532 (M⁺), 514, 356, 325, 297, 279, 161, 136, 135, 121, 91, 71, 61 (base peak)

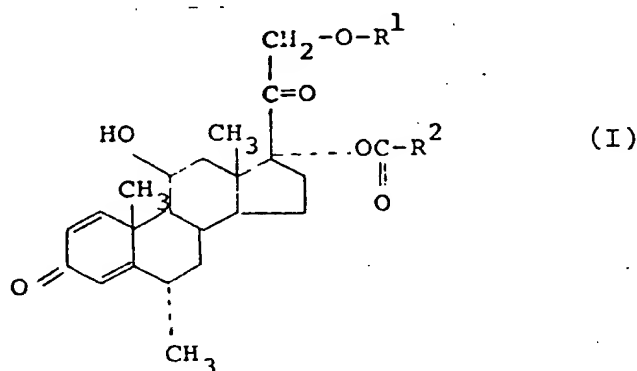
Elementary analysis (as C₂₉H₄₀O₇S)

Calc. (%): C 65.39 ; H 7.57

Found (%): C 65.47 ; H 7.49

CLAIMS:

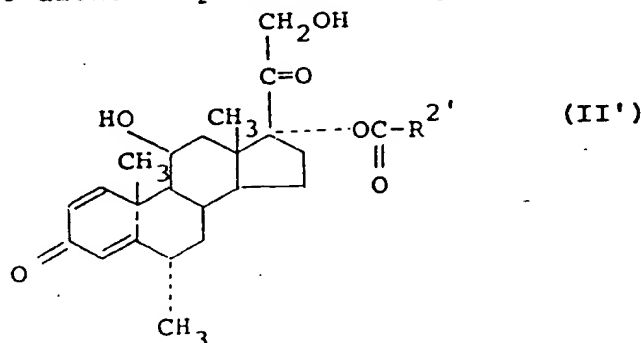
1. A 6 α -methylprednisolone derivative of the general formula:



wherein R¹ is a hydrogen atom or the group -C(=O)-R^3 where R³ is

a straight or once-branched chain C₁₋₄ alkyl group, a phenyl group or a lower alkoxy- or alkylthio-methyl group, and R² is a straight or once-branched chain C₁₋₄ alkyl group, a phenyl group or a lower alkoxy- or alkylthio-methyl group, with the proviso that when R² is ethyl group, R¹ is not a hydrogen atom or a propionyl group.

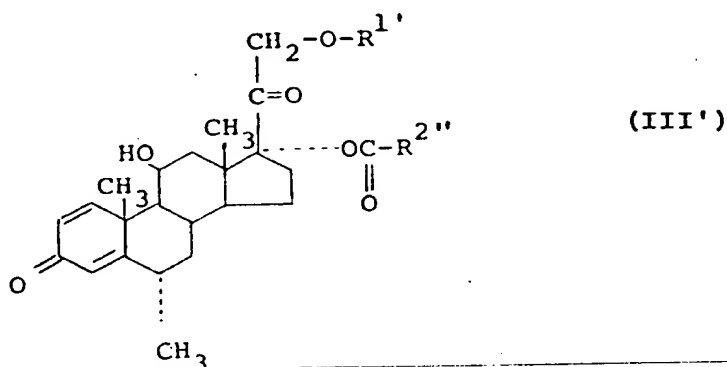
2. A 6 α -methylprednisolone derivative as claimed in claim 1 which is a 17 α -acyloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione compound of the general formula:



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wherein $R^{2'}$ is a straight or once-branched chain C_{3-4} alkyl group, a phenyl group or a lower alkoxy- or alkylthio-methyl group.

3. A 6α -methylprednisolone derivative as claimed in claim 1 which is a $17\alpha, 21$ -diacyloxy- 11β -hydroxy- 6α -methyl- $1,4$ -pregnadiene- $3,20$ -dione compound of the general formula:



15 wherein $R^{2''}$ is a straight or once-branched chain C_{1-4} group or a lower alkoxy- or alkylthio-methyl group, and $R^{1'}$ is the group $\text{--}\overset{\text{O}}{\underset{\text{O}}{\text{C}}}\text{--}R^3$ where R^3 is a straight or once-

20 branched chain C_{1-4} alkyl group, a phenyl group or a lower alkoxy- or alkylthio-methyl group, with the proviso that both R^3 and $R^{2''}$ are not ethyl groups.

4. A 6α -methylprednisolone derivative as claimed in claim 2 which is 17α -butyryloxy- $11\beta, 21$ -dihydroxy- 6α -methyl- $1,4$ -pregnadiene- $3,20$ -dione; 17α -isobutyryloxy- $11\beta, 21$ -dihydroxy- 6α -methyl- $1,4$ -pregnadiene- $3,20$ -dione; 17α -valeryloxy- $11\beta, 21$ -dihydroxy- 6α -methyl- $1,4$ -pregnadiene- $3,20$ -

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dione; 17 α -isovaleryloxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -benzoyloxy-11 β ,21-dihydroxy-6-methyl-1,4-pregnadiene-3,20-dione; 17 α -methoxyacetoxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; or 17 α -methylthioacetoxy-11 β ,21-dihydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione.

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5. A 6 α -methylprednisolone derivative as claimed in claim 3 which is 17 α ,21-diacetoxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -acetoxy-11 β -hydroxy-6 α -methyl-21-propionyloxy-1,4-pregnadiene-3,20-dione; 17 α -acetoxy-21-benzoyloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -acetoxy-11 β -hydroxy-6 α -methyl-21-valeryloxy-1,4-pregnadiene-3,20-dione; or 17 α -acetoxy-11 β -hydroxy-21-isovaleryloxy-6 α -methyl-1,4-pregnadiene-3,20-dione.

10

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6. A 6 α -methylprednisolone derivative as claimed in claim 3 which is 17 α -propionyloxy-21-acetoxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -propionyloxy-21-butyryloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -propionyloxy-21-isobutyryloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -propionyloxy-21-benzoyloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -propionyloxy-21-valeryloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -propionyloxy-21-isovaleryloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -propionyloxy-21-methoxyacetoxy-11 β -hydroxy-6 α -methyl-1,4-

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pregnadiene-3,20-dione; or 17 α -propionyloxy-21-methylthio-acetoxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione.

7. A 6 α -methylprednisolone derivative as claimed in
 5 claim 3 which is 17 α -butyryloxy-21-acetoxy-11 β -hydroxy-6 α -
 methyl-1,4-pregnadiene-3,20-dione; 17 α -butyryloxy-21-
 propionyloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-
 dione; 17 α ,21-dibutyryloxy-11 β -hydroxy-6 α -methyl-1,4-
 pregnadiene-3,20-dione; 17 α -butyryloxy-21-isobutyryloxy-11 β -
 10 hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -butyryloxy-
 21-methoxyacetoxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,
 20-dione; or 17 α -butyryloxy-21-methylthioacetoxy -11 β -hydroxy-
 6 α -methyl-1,4-pregnadiene-3,20-dione.

15 ~~8. A 6 α -methylprednisolone derivative as claimed in~~
 claim 3 which is 17 α -isobutyryloxy-21-acetoxy-11 β -hydroxy-6 α -
 -methyl-1,4-pregnadiene-3,20-dione; 17 α -isobutyryloxy-21-
 propionyloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-
 dione; 17 α -isobutyryloxy-21-butyryloxy-11 β -hydroxy-6 α -methyl-
 20 1,4-pregnadiene-3,20-dione; 17 α ,21-diisobutyryloxy-11 β -
 hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -isobutyry-
 loxy-21-methoxyacetoxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-
 3,20-dione; or 17 α -isobutyryloxy-21-methylthioacetoxy-11 β -
 hydroxy-6 α ,ethyl-1,4-pregnadiene-3,20-dione.

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9. A 6 α -methylprednisolone derivative as claimed in
 claim 3, which is 17 α -valeryloxy-21-acetoxy-11 β -hydroxy-6 α -

methyl-1,4-pregnadiene-3,20-dione; or 17 α -valeryloxy-21-propionyloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione.

5 10. A 6 α -methylprednisolone derivative as claimed
in claim 3, which is 17 α -isovaleryloxy-21-acetoxy-11 β -
hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; or 17 α -
isovaleryloxy-21-propionyloxy-11 β -hydroxy-6 α -methyl-1,4-
pregnadiene-3,20-dione.

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11. A 6 α -methylprednisolone derivative as claimed
in claim 3 which is 17 α -methoxyacetoxy-21-acetoxy-11 β -
hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -methoxy-
acetoxy-21-propionyloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-
15 3,20-dione; 17 α -methoxyacetoxy-21-butyryloxy-11 β -hydroxy-6 α -
-methyl-1,4-pregnadiene-3,20-dione; 17 α -methoxyacetoxy-21-
isobutyryloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-
dione; 17 α ,21-di(methoxyacetoxy)-11 β -hydroxy-6 α -methyl-1,4-
pregnadiene-3,20-dione; or 17 α -methoxyacetoxy-21-methyl-
20 thioacetoxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-
dione.

12. A 6 α -methylprednisolone derivative as claimed
in claim 3 which is 17 α -methylthioacetoxy-21-acetoxy-11 β -
25 hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -methyl-
thioacetoxy-21-propionyloxy-11 β -hydroxy-6 α -methyl-1,4-
pregnadiene-3,20-dione; 17 α -methylthioacetoxy-21-butyryloxy-

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11 β -hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; 17 α -
methyl-1,4-pregnadiene-3,20-dione; 17 α -methylthioacetox-
21-isobutyryloxy-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-
3,20-dione; 17 α -methylthioacetox-21-methoxyacetox-11 β -
5 hydroxy-6 α -methyl-1,4-pregnadiene-3,20-dione; or 17 α ,21-
di(methylthioacetox)-11 β -hydroxy-6 α -methyl-1,4-pregnadiene-
3,20-dione.

10 13. A pharmaceutical composition which comprises a
compound as claimed in any one of the preceding claims,
together with an inert carrier or diluent.

15 14. A pharmaceutical composition as claimed in
claim 13 which is in the form of an ointment, cream,
lotion, liquid, plaster or powder.



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EUROPEAN SEARCH REPORT

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Application number

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DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 2)
X	DE-A-2 144 405 (MERCK PATENT GmbH) * Claims; examples *	1-5	C 07 J 5/00 C 07 J 31/00 A 61 K 31/57
X,D	--- CHEMICAL ABSTRACTS, vol. 95, no. 24, 14th December 1981, page 378, no. 209651u, Columbus, Ohio, USA; & JP - A - 81 86119 (TAIHO YAKUHIN KOGYO K.K.) 13-07-1981 * Abstract *	1,13,14	
P,X	--- EP-A-O 072 547 (SCHERING AG) * Claims *	1,3,5-10,13,14	
P,X	--- EP-A-O 072 546 (SCHERING AG) * Claims 1,9-18,24 *	1,3,11,13,14	TECHNICAL FIELDS SEARCHED (Int. Cl. 2)
P,X	--- EP-A-O 072 200 (PLURICHEMIE ANSTALT) * Claim 1; pages 21,22, example 22 *	1,7,13,14	C 07 J 5/00 C 07 J 31/00

The present search report has been drawn up for all claims			
Place of search THE HAGUE		Date of completion of the search 02-10-1984	Examiner HENRY J.C.
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published n, r after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

(19)



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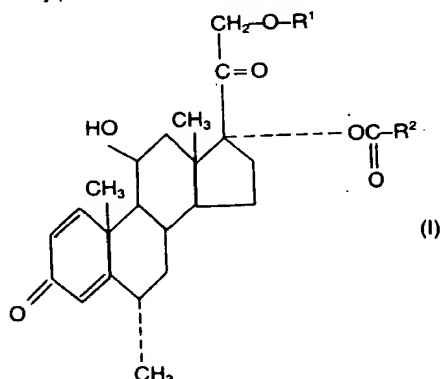
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(GB)(54) **6 Alpha-methylprednisolone derivatives.**(57) A 6 α -methylprednisolone derivative of the general formula:

wherein R¹ is a hydrogen atom or the group ---C---R^3 where R³ is a

straight or once-branched chain C₁₋₄ alkyl group, a phenyl group or a lower alkoxy- or alkylthio-methyl group, and R² is a straight or once-branched chain C₁₋₄ alkyl group, a phenyl group or a lower alkoxy- or alkylthio-methyl group, with the proviso that when R² is ethyl group, R¹ is not a hydrogen atom or a propionyl group.

These compounds exhibit a strong local anti-inflammatory effect and so are useful in external anti-inflammatory preparations for the treatment of various dermal disorders and also as anti-allergic drugs for the treatment of asthma and other allergic diseases.